(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 February 2008 (21.02.2008)

PCT

(10) International Publication Number
WO 2008/021432 A2

(51) International Patent Classification:
A61K 31/675 (2006.01) *A61K 31/554* (2006.01)

(21) International Application Number:
PCT/US2007/018138

(22) International Filing Date: 15 August 2007 (15.08.2007)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:

11/506,285	17 August 2006 (17.08.2006)	US
PCT/US2006/32405	17 August 2006 (17.08.2006)	US
60/904,206	1 March 2007 (01.03.2007)	US
11/809,470	1 June 2007 (01.06.2007)	US

(71) Applicant *(for all designated States except US)*: **THE TRUSTEES OF COLUMBIA UNIVERSITY IN THE CITY OF NEW YORK** [US/US]; 412 Low Memorial Library, 535 West 116th Street, New York, NY 10027 (US).

(72) Inventor; and

(75) Inventor/Applicant *(for US only)*: **MARKS, Andrew, Robert** [US/US]; 12 Locust Avenue, Larchmont, NY 10538 (US).

(74) Agents: **LOVE, Jane, M.** et al.; Wilmer Cutler Pickering Hale And Dorr LLP, 399 Park Avenue, New York, NY 10022 (US).

(81) Designated States *(unless otherwise indicated, for every kind of national protection available)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BH, BR, BW, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DO, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, GM, GT, HN, HR, HU, ID, IL, IN, IS, JP, KE, KG, KM, KN, KP, KR, KZ, LA, LC, LK, LR, LS, LT, LU, LY, MA, MD, ME, MG, MK, MN, MW, MX, MY, MZ, NA, NG, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RS, RU, SC, SD, SE, SG, SK, SL, SM, SV, SY, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, ZA, ZM, ZW.

(84) Designated States *(unless otherwise indicated, for every kind of regional protection available)*: ARIPO (BW, GH, GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IS, IT, LT, LU, LV, MC, MT, NL, PL, PT, RO, SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
— *without international search report and to be republished upon receipt of that report*

WO 2008/021432 A2

(54) Title: COMPOSITIONS AND METHODS FOR TREATMENT OF CONDITIONS AFFECTING THE NERVOUS SYSTEM

(57) Abstract: The present invention provides methods and compositions for the treatment and prevention of diseases, disorders, and conditions affecting the nervous system, such as neuropathies, seizures, and disorders affecting the cognitive functioning. The present invention also provides methods and compositions for improving cognitive function in the absence or presence of a specific cognitive disease, disorder or condition.

COMPOSITIONS AND METHODS FOR TREATMENT OF CONDITIONS AFFECTING THE NERVOUS SYSTEM

[0001] This application claims the benefit of priority of International Application PCT/US2006/32405 filed August 17, 2006; this application also claims the benefit of priority of U.S. Application No: 11/506,285 filed August 17, 2006; this application also claims the benefit of priority of U.S. Application No: 60/904,206 filed March 1, 2007; this application also claims the benefit of priority of U.S. Application No 11/809,470 filed June 1, 2007. The disclosures of these applications in their entirety are hereby incorporated by reference into this application. The text of all patent applications, published patents applications, issued and granted patents, and all references cited in this application are hereby incorporated by reference in their entirety. For example, in addition to the applications listed above, the contents of U.S. patent applications 09/568,474, 10/288,606, 10/680,988, 10/608,723, 10/809,089, 10/763,498, 10/794,218, 11/088,058, 11/088,123, 11/212,309, and 11/212,413, are hereby incorporated by reference in their entirety.

FIELD OF THE INVENTION

[0002] This invention relates to methods and compositions useful for the treatment and/or prevention of diseases, disorders and conditions affecting the nervous system, such as neuropathies, seizures, and disorders affecting cognitive functioning.

BACKGROUND OF THE INVENTION

[0003] Ryanodine receptors (RyRs) are channels that open and close to regulate the release of Ca^{2+} from intracellular stores into cytoplasm of the cell. The "open probability" (Po) of a RyR receptor refers to the likelihood that the RyR channel is open at any given moment, and therefore capable of releasing Ca^{2+} into the cytoplasm.

[0004] There are three types of ryanodine receptors, all of which are Ca^{2+} channels: RyR1, RyR2, and RyR3. RyR1 is found predominantly in skeletal muscle as well as other tissues, RyR2 is found predominantly in the heart as well as other tissues, and RyR3 is found in the brain as well as other tissues. All three isoforms of RyRs (RyR1, RyR2 and RyR3) are expressed in the central nervous system (CNS) (Furuichi et al., (1994) J Neurosci, 14, 4794–4805 "Multiple types of ryanodine receptor/Ca2+ release channels are differentially expressed in rabbit brain; Giannini et al., (1995) J Cell Biol, 128, 893–904. "The ryanodine receptor/calcium channel genes are widely and differentially expressed in murine brain and

peripheral tissues"). In the brain, RyR2 is expressed at robust levels while RyR1 and RyR3 contribute a smaller fraction of total RyRs in neurons. The three RyR isoforms differ in their pattern of expression in distinct areas of the brain (Furuichi et al., 1994; Giannini et al., 1995). For instance, RyR1 is preferentially expressed in Purkinje cells, while RyR2 is expressed in cerebellar granule cells as well as other areas of the brain. RyR3 is expressed in the hippocampal CA1 pyramidal cell layer, the caudate/putamen, the olfactory bulb and olfactory tubercle, as well as other brain regions. RyR immunostaining has been observed in cell bodies, axons, dendrites, spines and dendritic shafts of neurons (See Sharp et al., (1993) J Neurosci, 13, 3051–3063 "Differential immunohistochemical localization of inositol, 1,4,5,-trisphosphate- and ryanodine-sensitive Ca2+ release channels in rat brain." See also Berridge, (1998) Neuron, 21, 13–26. "Neuronal calcium signaling").

[0005] RyRs have been shown to be involved in learning and memory. For example, deletion of RyR3 in knockout mice has been shown to impair forms of synaptic plasticity and spatial learning (Balschun et al., EMBO Journal (1999) 18, 5264–5273 "Deletion of the ryanodine receptor type 3 (RyR3) impairs forms of synaptic plasticity and spatial learning"). Kohda et al. found that Ca2+ release from ryanodine-sensitive Ca2+ stores is required for the induction of long term depression "LTD" in cultured cerebellar Purkinje cells. (Khoda et al. (1995) J Neurophysiol, 74, 2184–2188 "Ca^{2+} release from Ca^{2+} stores, particularly from ryanodine-sensitive Ca^{2+} stores, is required for the induction of LTD in cultured cerebellar Purkinje cells.") Others have shown that RyR2 may also be involved in memory processing after spatial learning. See Zhao et al., FASEB Journal. 2000;14:290-30 "Spatial learning induced changes in expression of the ryanodine type II receptor in the rat hippocampus."

[0006] Some studies have also suggested that RyRs may be involved in seizure conditions such as epilepsy, and that inhibition of RyRs may also have neuroprotective effects – inhibiting neuronal cell death . Thus, Yoshida et al. concluded that "indirect inhibition of RyR activities by [the drug] ZNS during neuronal hyperexcitability appear[s] to be involved in the mechanisms of action of antiepileptic and neuroprotective actions of ZNS." See Yoshida at al. (2005) Epilepsy Res. Dec;67(3):153-62. "Effects of zonisamide on neurotransmitter exocytosis associated with ryanodine receptors." Others have found that the "Ca2+ contributed from ryanodine-sensitive stores (i.e., Ca2+-induced Ca2+ release), may be necessary for seizure-induced cell death," see Pelletier et al. (1999) J Neurophysiol. Jun;81(6):3054-64 "Seizure-induced cell death produced by repeated tetanic stimulation in

vitro: possible role of endoplasmic reticulum calcium stores." See also, Mori et al., Epilepsy Res. (2005) Jun;65(1-2):59-70 "Effects of ryanodine receptor activation on neurotransmitter release and neuronal cell death following kainic acid-induced status epilepticus."

[0007] RyR channels are formed by four RyR polypeptides in association with four FK506 binding proteins (FKBPs), specifically FKBP12 (calstabin1) and FKBP12.6 (calstabin2). Calstabin1 binds to RyR1, calstabin2 binds to RyR2, and calstabin1 binds to RyR3. The FKBP proteins (calstabin1 and calstabin2) bind to the RyR channel (one molecule per RyR subunit), stabilize RyR-channel functioning, and facilitate coupled gating between neighboring RyR channels, thereby preventing abnormal activation of the channel during the channel's closed state.

[0008] The function of RyRs is also regulated by phosphorylation. PKA phosphorylation of RyRs causes partial dissociation of calstabins from RyRs. Dissociation of calstabin from RyR increases the open probability of RyRs, and thereby increases Ca^{2+} release into the cytoplasm.

SUMMARY OF THE INVENTION

[0009] The present invention is based, in part, on the discovery that certain 1,4, benzothiazepine compounds are able to cross the blood brain barrier and stabilize RyR calcium channels in the brain by increasing binding and/or preventing depletion of calstabin from the RyR channels during stress and other conditions that modify the channel. The increase in binding or prevention of depletion of calstabin from the RyR channels contributes to improved cognitive function *in vivo*. Thus, the present invention provides methods and compositions for the treatment and prevention of diseases, disorders and conditions associated with abnormal RyR function in the nervous system, such as neuropathies, seizures, and disorders affecting cognitive functioning.

[0010] In certain embodiments, the present invention is directed to methods of treating or preventing diseases, disorders, and conditions affecting the nervous system, such as neuropathies, seizures, or cognitive dysfunction conditions, in a subject in need thereof, comprising administering to the subject a therapeutically or prophylactically effective amount of a compound of Formula I, as described herein, or enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, or pro-drugs thereof, or any combination thereof. In some embodiments, the compound of Formula I is

represented by the structure of any one or more of Formula I-a, I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-i, I-j, I-k, I-l, I-m, I-n, I-o, I-p, or Formula II, or enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, or pro-drugs thereof, or any combination thereof.

[0011] In certain preferred embodiments, the compound administered is selected from the group consisting of S1, S2, S3, S4, S5, S6, S7, S9, S11, S12, S13, S14, S19, S20, S22, S23, S24, S25, S26, S27, S36, S37, S38, S40, S43, S44, S45, S46, S47, S48, S49, S50, S51, S52, S53, S54, S55, S56, S57, S58, S59, S60, S61, S62, S63, S64, S66, S67, S68, S69, S70, S71, S72, S73, S74, S75, S76, S77, S78, S79, S80, S81, S82, S83, S84, S85, S86, S87, S88, S89, S90, S91, S92, S93, S94, S95, S96, S97, S98, S99, S100, S101, S102, S103, S104, S105, S107, S108, S109, S110, S111, S112, S113, S114, S115, S116, S117, S118, S119, S120, S121, S122, and S123.

[0012] In further preferred embodiments, the compound administered is selected from the group consisting of S101, S102, S103, S104, S105, S107, S108, S109, S110, S111, S112, S113, S114, S115, S116, S117, S118, S119, S120, S121, S122, and S123.

[0013] In a particularly preferred embodiment, the compound administered is S107.

[0014] In other embodiments, the present invention provides a method of treating or preventing diseases, disorders, and conditions affecting the nervous system, such as neuropathies, seizures, or cognitive dysfunction conditions, in a subject in need thereof, comprising administering to the subject a therapeutically or prophylactically effective amount of a compound that decreases the open probability of a RyR channel.

[0015] In yet another embodiment, the present invention provides a method of treating or preventing diseases, disorders, and conditions affecting the nervous system, such as neuropathies, seizures, or cognitive dysfunction conditions, in a subject in need thereof, comprising administering to the subject a therapeutically or prophylactically effective amount of a compound that decreases Ca2+ current through a RyR channel.

[0016] In a further embodiment, the present invention provides a method of treating or preventing diseases, disorders, and conditions affecting the nervous system, such as neuropathies, seizures, or cognitive dysfunction conditions, in a subject in need thereof,

comprising administering to the subject a therapeutically or prophylactically effective amount of a compound that decreases calcium leak through a RyR channel.

[0017] In an additional embodiment, the present invention provides a method of treating or preventing diseases, disorders, and conditions affecting the nervous system, such as neuropathies, seizures, or cognitive dysfunction conditions, in a subject in need thereof, comprising administering to the subject a therapeutically or prophylactically effective amount of a compound that increases the affinity with which a calstabin binds to a RyR.

[0018] In other embodiments, the present invention provides a method of treating or preventing diseases, disorders, and conditions affecting the nervous system, such as neuropathies, seizures, or cognitive dysfunction conditions, in a subject in need thereof, comprising administering to the subject a therapeutically or prophylactically effective amount of a compound that decreases dissociation of a calstabin from a RyR.

[0019] In other embodiments, the present invention provides a method of treating or preventing diseases, disorders, and conditions affecting the nervous system, such as neuropathies, seizures, or cognitive dysfunction conditions, in a subject in need thereof, comprising administering to the subject a therapeutically or prophylactically effective amount of a compound that increases rebinding of a calstabin to a RyR.

[0020] In certain embodiments, the subject to whom the compounds of the invention are administered is a mammal selected from the group consisting of primates, rodents, ovine species, bovine species, porcine species, equine species, feline species and canine species. In a preferred embodiment, the subject is a human.

[0021] In certain embodiments, the subject is suffering from, or at risk of developing, a neuropathy, such as a peripheral neuropathy or a central neuropathy. For example, the subject may be suffering, or at risk of developing, a neuropathy selected from the group consisting of vestibular neuropathy, optic neuropathy, optic nerve neuropathy, retinal neuropathy, diabetic neuropathy, alcoholic neuropathy, and neuropathy caused by Charcot-Marie-Tooth disease (CMT), Friedreich's ataxia, Gullain-Barre syndrome, polyarteritis nodosa, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis, sjogren syndrome, HIV infection, syphhilis infection, herpes infection, hepatitis infection, colorado tick fever infection, diptheria infection, leprosy, Lyme disease, bacterial infection, viral infection, inflammatory processes, exposure to toxins, treatment with drugs, treatment with

chemotherapeutic drugs, cancer, nutritional deficiency, vitamin B-12 deficiency, thiamine deficiency, trauma, pressure on a nerve, a heritable condition, demyelination, axonal damage, uremia, amyloidosis, arsenic poisoning, nitrous oxide exposure or heavy metal exposure.

[0022] In certain embodiments, the subject is suffering from, or at risk of developing, epilepsy or non-epileptic seizures. For example, the subject may be suffering, or at risk of developing, a condition selected from the group consisting of epilepsy, partial onset seizures, focal onset seizures, distributed seizures, generalized seizures, simple partial seizures, complex partial seizures, myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures, atonic seizures, petit mal seizures, grand mal seizures, Jacksonian seizures, psychomotor seizures, temporal-lobe seizures, non-epileptic seizures, unprovoked seizures, alcoholic seizures, infantile spasms, West syndrome, benign childhood epilepsy with centro-temporal spikes, benign rolandic epilepsy, benign childhood epilepsy with occipital paroxysms, juvenile myoclonic epilepsy (JME), temporal lobe epilepsy, frontal lobe epilepsy, Lennox-Gastaut syndrome, occipital lobe epilepsy, fetal alcohol spectrum disorder (FASD), psychogenic seizures, and febrile convulsions.

[0023] In certain embodiments, the subject is suffering from, or at risk of developing, a cognitive disorder. For example, the subject may be suffering, or at risk of developing, a cognitive disorder selected from the group consisting of dementia, delirium, amnesia, aphasia, Alzheimer's disease, vascular dementia, multi-infarct dementia, Binswanger's disease, dementia with Lewy bodies (DLB), alcohol-induced persisting dementia, frontotemporal lobar degenerations (FTLD), Pick's disease, frontotemporal dementia, frontal variant FTLD, semantic dementia, temporal variant FTLD, progressive non-fluent aphasia, Creutzfeldt-Jakob disease, Huntington's disease, Parkinson's disease, AIDS dementia complex, an attention disorder, attention-deficit disorder (ADD), attention-deficit hyperactivity disorder (ADHD), age-related cognitive dysfunction and stress-induced cognitive dysfunction including post-traumatic stress disorder.

[0024] In other embodiments the present invention provides compositions and methods for improving cognitive function in a subject who is does not have a discernable cognitive disease, disorder or condition. All of the above listed methods, compounds, delivery routes, and doses may be used for such purposes. For example, the compounds and methods of the invention may be used to improve cognitive function (such as memory (long and/or or short

term), learning, attention or other cognitive functions) in an subject, whether young or aging, who is not suffering from a discernable cognitive disease, disorder or condition.

[0025] The compounds of the invention may be administered by any suitable route known in the art, without limitation. For example, compounds of the invention may be administered by a route selected from the group consisting of parenteral, enteral, intravenous, intraarterial, intracardiac, intra intrapericardial, intraosseal, intracutaneous, subcutaneous, intradermal, subdermal, transdermal, intrathecal, intramuscular, intraperitoneal, intrasternal, parenchymatous, oral, sublingual, buccal, rectal, vaginal, inhalational, and intranasal. Additionally, the compounds of the invention may be administered using a drug-releasing implant.

[0026] In one preferred embodiment, the compounds of the invention are administered to the subject at a dose sufficient to restore binding of a calstabin to a RyR, or prevent depletion of calstabin from RyR, or at a dose sufficient to enhance binding of a calstabin to a RyR. In certain non-limiting embodiments, the compounds of the invention are administered to the subject a dose of from about 0.01 mg/kg/day to about 20 mg/kg/day, or more preferably still, at a dose of from about 0.05 mg/kg/day to about 1 mg/kg/day.

[0027] Other features and advantages of the present invention will become apparent from the following description. It should also be understood that various changes and modifications to the methods and compositions described herein are possible without departing from the spirit and scope of the invention. Variations and modifications that can be made without departing from the spirit and scope of the invention will be apparent to those skilled in the art, and all such variations and modifications are within the scope of the invention. For example, further variations and modifications of the invention may be made in accordance with the description provided in U.S. patent applications 09/568,474, 10/288,606, 10/680,988, 10/608,723, 10/809,089, 10/763,498, 10/794,218, 11/088,058, 11/088,123, 11/212,309, 11/506,285, and 11/212,413, the contents of which are hereby incorporated by reference in their entirety.

BRIEF DESCRIPTION OF THE FIGURES

[0028] Figure 1 provides data illustrating that the compound S107 crosses the blood brain barrier and enhances binding of calstabin to a RyR in the brain (mid-section and cerebellum) *in vivo*. Data from heart and soleus muscle are also illustrated.

[0029] Figure 2 provides a schematic representation of an experimental protocol used to test the effect of S107 on exercise performance and spatial learning in mice.

[0030] Figure 3 shows the difference in permanence time between S107 and vehicle treated mice. A: schematic representation of platform. B: latency to target(s) for vehicle (veh) and S107 treated mice. C: mean velocity (cm/s) for vehicle (veh) and S107 treated mice.

[0031] Figure 4 shows a trend towards altered behavior consistent with improved learning and persistence in S107-treated mice (C), as compared with vehicle-treated mice (B). Panel A provides a schematic representation of the platform.

[0032] Figure 5 B is a bar graph representation showing improved learning or increased persistence with S107 treated mice, as compared with vehicle. Panel A provides a schematic representation of the experimental set-up.

[0033] Figure 6 is an immunoblot showing total RyR (types 1 and 2), phosphorylated RyR and calstabin (types 1 and 2) in control mice and mice subjected to an exercise regimen, with or without treatment with S107. Whole brain microsomess were obtained. Immunoprecipitates were separated by 4-20% PAGE and analyzed for total RyR, PKA phosphorylated RyR, and calstabin.

[0034] Figure 7 provides a schematic representation of a protocol for evaluating the effects of restraint stress on PKA phosphorylation at different stress periods.

[0035] Figure 8 shows PKA phosphorylation of RyR2 channels in brain following restraint induced stress in mice. Mice were restrained for time periods indicated. Ryanodine receptor (type2) was immunoprecipitated from whole brain microsomes. Immunoprecipitates were separated by 4-20% PAGE and analyzed for total RyR2, PKA phosphorylated RyR2, and calstabin2.

[0036] Figure 9 shows the effect of chronic restraint stress (CRS) on relative PKA phosphorylation of RyR2 in brain. Total RyR2 and PKA phosphorylated RyR2 were quantified by densitometry of the immunoblot shown in Figure 8. The bar graphs represent the relative PKA phosphorylation of the RyR2 channel, as determined by dividing the phosphorylation signal by the RyR2 signal. (*** $P < 0.001$; ** $P < 0.01$).

[0037] Figure 10 shows the effects of chronic restraint stress (CRS) on calstabin2 binding to RyR2 in the brain. Total RyR2 and calstabin2 were quantified by densitometry of the immunoblot shown in Figure 8. The bar graphs represent the relative amount of calstabin2 in the immunoprecipitate and were determined by dividing the calstabin signal by the RyR2 signal. (* $P < 0.05$).

DETAILED DESCRIPTION OF THE INVENTION

Definitions

[0038] The following are definitions of some of the terms used in the present specification. Other terms are defined elsewhere in the specification. The initial definition provided for a chemical group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated.

[0039] As used herein and in the appended claims, the singular forms "a," "an," and "the" include plural references unless the content clearly dictates otherwise. Thus, for example, reference to "an agent" or "a compound" includes a plurality of such agents or compounds and equivalents thereof known to those skilled in the art.

[0040] As used herein, the term "RyCal compounds" refers to compounds of the general I-a, I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-i, I-j, I-k, I-l, I-m, I-n, I-o, I-p, or Formula II, or enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, or pro-drugs thereof, or any combination thereof, and herein also referred to as "compound(s) of the invention".

[0041] The compounds of the invention are referred to using a numerical naming system, with compound numbers 1 to 123 provided herein. These numbered compounds are referred to using either the prefix "S" or the prefix "ARM." Thus, the first numbered compound is referred to either as "S1" or "ARM001", the second numbered compound is referred to as either "S2" or "ARM002", the third numbered compound is referred to as either "S3" or "ARM003", and so on. The "S" and the "ARM" nomenclature systems are used interchangeably throughout the specification, the drawings, and the claims.

[0042] The term "alkyl" as used herein refers to a linear or branched, saturated hydrocarbon having from 1 to 6 carbon atoms. Representative alkyl groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, pentyl, isopentyl, neopentyl,

hexyl, isohexyl, and neohexyl. The term "C_1-C_4 alkyl" refers to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 4 carbon atoms, such as methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, and isobutyl.

[0043] The term "alkenyl" as used herein refers to a linear or branched hydrocarbon having from 2 to 6 carbon atoms and having at least one carbon-carbon double bond. In one embodiment, the alkenyl has one or two double bonds. The alkenyl moiety may exist in the E or Z conformation and the compounds of the present invention include both conformations.

[0044] The term "alkynyl" as used herein refers to a linear or branched hydrocarbon having from 2 to 6 carbon atoms and having at least one carbon-carbon triple bond.

[0045] The term "aryl" as used herein refers to an aromatic group containing 1 to 3 aromatic rings, either fused or linked.

[0046] The term "cyclic group" as used herein includes a cycloalkyl group and a heterocyclic group.

[0047] The term "cycloalkyl group" as used herein refers to a three- to seven-membered saturated or partially unsaturated carbon ring. Any suitable ring position of the cycloalkyl group may be covalently linked to the defined chemical structure. Exemplary cycloalkyl groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, and cycloheptyl.

[0048] The term "halogen" as used herein refers to fluorine, chlorine, bromine, and iodine.

[0049] The term "heterocyclic group" or "heterocyclic" or "heterocyclyl" or "heterocyclo" as used herein refers to fully saturated, or partially or fully unsaturated, including aromatic (i.e., "heteroaryl") cyclic groups (for example, 4 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 16 membered tricyclic ring systems) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3, or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. The heterocyclic group may be attached to the remainder of the molecule at any heteroatom or carbon atom of the ring or ring system. Exemplary heterocyclic groups include, but are not limited to, azepanyl, azetidinyl, aziridinyl, dioxolanyl, furanyl, furazanyl, homo piperazinyl, imidazolidinyl,

imidazolinyl, isothiazolyl, isoxazolyl, morpholinyl, oxadiazolyl, oxazolidinyl, oxazolyl, oxazolidinyl, pyrimidinyl, phenanthridinyl, phenanthrolinyl, piperazinyl, piperidinyl, pyranyl, pyrazinyl, pyrazolidinyl, pyrazolinyl, pyrazolyl, pyridazinyl, pyridooxazolyl, pyridoimidazolyl, pyridothiazolyl, pyridinyl, pyrimidinyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, tetrahydrofuranyl, thiadiazinyl, thiadiazolyl, thienyl, thienothiazolyl, thienooxazolyl, thienoimidazolyl, thiomorpholinyl, thiophenyl, triazinyl, and triazolyl. Exemplary bicyclic heterocyclic groups include indolyl, isoindolyl, benzothiazolyl, benzoxazolyl, benzoxadiazolyl, benzothienyl, quinuclidinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, benzofurazanyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydroisoindolyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), triazinylazepinyl, tetrahydroquinolinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, acridinyl, phenanthridinyl, xanthenyl and the like.

[0050] The term "phenyl" as used herein refers to a substituted or unsubstituted phenyl group.

[0051] The aforementioned terms "alkyl," "alkenyl," "alkynyl," "aryl," "phenyl," "cyclic group," "cycloalkyl," "heterocyclyl," "heterocyclo," and "heterocycle" may further be optionally substituted with one or more substituents. Exemplary substituents include but are not limited to one or more of the following groups: hydrogen, halogen, CF_3, OCF_3, cyano, nitro, N_3, oxo, cycloalkyl, alkenyl, alkynyl, heterocycle, aryl, alkylaryl, heteroaryl, OR_a, SR_a, $S(=O)R_e$, $S(=O)_2R_e$, $P(=O)_2R_e$, $S(=O)_2OR_a$, $P(=O)_2OR_a$, NR_bR_c, $NR_bS(=O)_2R_e$, $NR_bP(=O)_2R_e$, $S(=O)_2NR_bR_c$, $P(=O)_2NR_bR_c$, $C(=O)OR_a$, $C(=O)R_a$, $C(=O)NR_bR_c$, $OC(=O)R_a$, $OC(=O)NR_bR_c$, $NR_bC(=O)OR_a$, $NR_dC(=O)NR_bR_c$, $NR_dS(=O)_2NR_bR_c$, $NR_dP(=O)_2NR_bR_c$, $NR_bC(=O)R_a$, or $NR_bP(=O)_2R_e$, wherein R_a is hydrogen, alkyl, cycloalkyl, alkenyl, alkynyl, alkylaryl, heteroaryl, heterocycle, or aryl; R_b, R_c and R_d are independently hydrogen, alkyl, cycloalkyl, alkylaryl, heteroaryl, heterocycle, aryl, or said R_b and R_c together with the N to which they are bonded optionally form a heterocycle; and R_e is alkyl, cycloalkyl, alkenyl, cycloalkenyl, alkynyl, alkylaryl, heteroaryl, heterocycle, or aryl. In the aforementioned exemplary substitutents, groups such as alkyl, cycloalkyl, alkenyl, alkynyl, cycloalkenyl, alkylaryl, heteroaryl, heterocycle and aryl can themselves be optionally substituted.

[0052] Exemplary substituents may further optionally include at least one labeling group, such as a fluorescent, a bioluminescent, a chemiluminescent, a colorimetric and a radioactive labeling group. A fluorescent labeling group can be selected from bodipy, dansyl, fluorescein, rhodamine, Texas red, cyanine dyes, pyrene, coumarins, Cascade Blue™, Pacific Blue, Marina Blue, Oregon Green, 4',6-Diamidino-2-phenylindole (DAPI), indopyra dyes, lucifer yellow, propidium iodide, porphyrins, arginine, and variants and derivatives thereof. For example, ARM118 of the present invention contains a labeling group BODIPY, which is a family of fluorophores based on the 4,4-difluoro-4-bora-3a,4a-diaza-*s*-indacene moiety. For further information on fluorescent label moieties and fluorescence techniques, see, e.g., *Handbook of Fluorescent Probes and Research Chemicals*, by Richard P. Haughland, Sixth Edition, Molecular Probes, (1996), which is hereby incorporated by reference in its entirety. One of skill in the art can readily select a suitable labeling group, and conjugate such a labeling group to any of the compounds of the invention, without undue experimentation.

[0053] The term "quaternary nitrogen" refers to a tetravalent positively charged nitrogen atom including, for example, the positively charged nitrogen in a tetraalkylammonium group (e.g., tetramethylammonium, N-methylpyridinium), the positively charged nitrogen in protonated ammonium species (e.g., trimethyl-hydroammonium, N-hydropyridinium), the positively charged nitrogen in amine N-oxides (e.g., N-methyl-morpholine-N-oxide, pyridine-N-oxide), and the positively charged nitrogen in an N-amino-ammonium group (e.g., N-aminopyridinium).

[0054] Throughout the specification, unless otherwise noted, the nitrogen in the benzothiazepine ring of compounds of the present invention may optionally be a quaternary nitrogen. Non-limiting examples include ARM-113 and ARM-119.

[0055] Compounds of the present invention may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

[0056] The term "compound(s) of the invention" as used herein means a compound of Formula I-a, I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-i, I-j, I-k, I-l, I-m, I-n, I-o, I-p, or Formula II, or enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, or pro-drugs thereof, or any combination thereof.

[0057] A "pharmaceutical composition" refers to a mixture of one or more of the compounds described herein, or pharmaceutically acceptable salts, hydrates or pro-drugs thereof, with other chemical components, such as physiologically acceptable carriers and excipients. The purpose of a pharmaceutical composition is to facilitate administration of a compound to an organism.

[0058] A "pro-drug" refers to an agent which is converted into the parent drug *in vivo*. Pro-drugs are often useful because, in some situations, they are easier to administer than the parent drug. They are bioavailable, for instance, by oral administration whereas the parent drug is not. The pro-drug also has improved solubility in pharmaceutical compositions over the parent drug. For example, the compound carries protective groups which are split off by hydrolysis in body fluids, *e.g.*, in the bloodstream, thus releasing active compound or is oxidized or reduced in body fluids to release the compound.

[0059] A compound of the present invention also can be formulated as a pharmaceutically acceptable salt, *e.g.*, acid addition salt, and complexes thereof. The preparation of such salts can facilitate the pharmacological use by altering the physical characteristics of the agent without preventing its physiological effect. Examples of useful alterations in physical properties include, but are not limited to, lowering the melting point to facilitate transmucosal administration and increasing the solubility to facilitate administering higher concentrations of the drug.

[0060] The term "pharmaceutically acceptable salt" means an acid addition salt that is suitable for, or compatible with, the treatment of a patient or a subject such as a human patient. The salts can be any non-toxic organic or inorganic salt of any of the compounds represented by Formula I, I-a, I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-i, I-j, I-k, I-l, I-m, I-n, I-o, I-p or any of the specific compounds described herein, or any of their intermediates. Illustrative inorganic acids that form suitable salts include, but are not limited to, hydrochloric, hydrobromic, sulfuric and phosphoric acids. Illustrative organic acids that form suitable acid addition salts include, but are not limited to, mono-, di-, and tricarboxylic acids such as glycolic, lactic, pyruvic, malonic, succinic, glutaric, fumaric, malic, tartaric, citric, ascorbic, maleic, benzoic, phenylacetic, cinnamic and salicylic acids, as well as sulfonic acids such as p-toluene sulfonic and methanesulfonic acids. Illustrative salt-forming ions include, but are not limited to, ammonium (NH4+), calcium (Ca2+), iron (Fe2+ and Fe3+), magnesium (Mg2+), potassium (K+), pyridinium (C5H5NH+), quaternary ammonium (NR4+), sodium

(Na+), acetate, carbonate, chloride, bromide, citrate, cyanide, hydroxide, nitrate, nitrite, oxide, phosphate, sulfate, maleate, fumarate, lactate, tartrate, gluconate, besylate, and valproate. The salts formed can be either mono or di-acid salts can be formed, and such salts exist in either a hydrated, solvated or substantially anhydrous form, or metal salts such as sodium monohydrogen orthophosphate and potassium hydrogen sulfate. In general, the acid addition salts of compounds of the invention are more soluble in water and various hydrophilic organic solvents, and generally demonstrate higher melting points in comparison to their free base forms. The selection of an appropriate salt can be performed by one skilled in the art. For example, one can select salts in reference to "Handbook of Pharmaceutical Salts : Properties, Selection, and Use" by P. Heinrich Stahl and Camille G. Wermuth, or Berge (1977) "Pharmaceutcial Salts" J. Pharm Sci., Vol 66(1), p 1-19. Other non-pharmaceutically acceptable salts (e.g., oxalates) may be used, for example, in the isolation of compounds of the invention for laboratory use or for subsequent conversion to a pharmaceutically acceptable acid addition salt.

[0061] The compounds of the present invention form hydrates or solvates, which are included in the scope of the claims. When the compounds of the present invention exist as regioisomers, configurational isomers, conformers or diasteroisomeric forms all such forms and various mixtures thereof are included in the scope of the compounds of the invention. It is possible to isolate individual isomers using known separation and purification methods, if desired. For example, when a compound of the present invention is a racemate, the racemate can be separated into the (S)-compound and (R)-compound by optical resolution. Individual optical isomers and mixtures thereof are included in the scope of the invention.

[0062] The term "solvate" as used herein means a compound of Formula I, I-a, I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-i, I-j, I-k, I-l, I-m, I-n, I-o, I-p, or Formula II, or a pharmaceutically acceptable salt thereof, wherein molecules of a suitable solvent are incorporated in the crystal lattice. A suitable solvent is physiologically tolerable at the dosage administered. Examples of suitable solvents are ethanol, water and the like. When water is the solvent, the molecule is referred to as a "hydrate."

[0063] The term "complex" as used herein refers to an entity composed of molecules in which the constituents maintain much of their chemical identity.

[0064] The term "metabolite" as used herein refers to a byproduct produced *in vivo*, for example in a subject, from a chemical compound.

[0065] The terms an "effective amount," "sufficient amount," "therapeutically effective amount," or "prophylactically effective" amount" of an agent or compounds, as used herein, refer to amounts sufficient to effect the beneficial or desired results, including clinical results and, as such, the actual "amount" intended will depend upon the context in which it is being applied, such as whether the desired clinical outcome is prevention or treatment. The term "effective amount" also includes that amount of the compound of Formula I, I-a, I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-i, I-j, I-k, I-l, I-m, I-n, I-o, I-p, or Formula II, which is "therapeutically effective" or "prophylactically effective" and which avoids or substantially attenuates undesirable side effects.

[0066] As used herein and as well understood in the art, "treatment" is an approach for obtaining beneficial or desired results, including clinical results. Beneficial or desired clinical results can include, but are not limited to, alleviation or amelioration of one or more symptoms or conditions, diminishment of extent of disease, stabilized (*i.e.*, not worsening) state of disease, preventing spread of disease, delay or slowing of disease progression, amelioration or palliation of the disease state and remission (whether partial or total), whether detectable or undetectable. "Treatment" can also mean prolonging survival as compared to expected survival if not receiving treatment. Unless otherwise stated, the term "treatment" should be construed as encompassing preventive and therapeutic methods.

[0067] The terms "animal," "subject" and "patient" as used herein include all members of the animal kingdom including, but not limited to, mammals, animals (*e.g.*, cats, dogs, horses, etc.) and humans.

[0068] All stereoisomers of the compounds of the present invention (for example, those which may exist due to asymmetric carbons on various substituents), including enantiomeric forms and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers (e.g., as a pure or substantially pure optical isomer having a specified activity), or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention may have the S or R configuration as defined by the IUPAC 1974 Recommendations. The racemic forms can be

resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by any suitable method, including without limitation, conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

[0069] Compounds useful in the present invention are, subsequent to their preparation, preferably isolated and purified to obtain a composition containing an amount by weight equal to or greater than 99% of the compound ("substantially pure" compound), which is then used or formulated as described herein. Such "substantially pure" compounds of the present invention are also contemplated herein as part of the present invention.

[0070] All configurational isomers of the compounds of the present invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds of the present invention embraces both cis (*Z*) and trans (*E*) alkene isomers, as well as cis and trans isomers of cyclic hydrocarbon or heterocyclic rings.

Neuropathies

[0071] In one aspect, the present invention is directed to compositions and methods for the treatment and prevention of neuropathies. The term "neuropathy" as used herein refers to conditions characterized by damage to the nerves, including, but not limited to, damage caused by infections, inflammatory processes, exposure to toxins, treatment with drugs, nutritional deficiency, trauma, pressure on a nerve, neuronal death, neuronal degeneration, and heritable conditions. Although the term "neuropathy" is most frequently used to refer to conditions characterized damage to the peripheral nerves, i.e. "peripheral neuropathies", as used herein, the term "neuropathy" includes both peripheral neuropathies and neuropathies affecting nerves of the central nervous system, i.e. "central neuropathies."

[0072] There are various sub-classifications of neuropathies. For example, neuropathies may be classified as either peripheral or central, as either acute or chronic, or as either demyelinating or axonal. Neuropathies may also be classified according to the number of nerves that they affect. A neuropathy may involve damage to only a single nerve or nerve group (referred to as mononeuropathies) or may affect multiple nerves (polyneuropathies).

[0073] Peripheral neuropathies may be caused by hereditable disorders, systemic or metabolic disorders, dietary deficiencies, exposure to toxic substances, treatment with drugs, infection, inflammatory response, autoimmune diseases, and multiple other factors. Also, many peripheral neuropathies are of unknown etiology.

[0074] Examples of hereditable peripheral neuropathies include, but are not limited to, Charcot-Marie-Tooth disease (CMT) and Friedreich's ataxia,

[0075] Examples of peripheral neuropathies caused by systemic or metabolic disorders include, but are not limited to diabetic neuropathy.

[0076] Examples of peripheral neuropathies caused by dietary deficiencies include, but are not limited to neuropathy caused by vitamin B-12 deficiency, and neuropathy caused by thiamine deficiency.

[0077] Examples of peripheral neuropathies caused by exposure to toxic substances include, but are not limited to neuropathy caused by excessive alcohol use ("alcoholic neuropathy"), neuropathy caused by uremia (such as in kidney failure patients), neuropathy caused by arsenic, neuropathy caused by nitrous oxide, neuropathy caused by industrial agents especially solvents, neuropathy caused by heavy metal exposure (such as lead, arsenic, mercury, and the like)

[0078] Examples of peripheral neuropathies caused by infectious agents and/or inflammatory or autoimmune processes include, but are not limited to, neuropathies caused by Gullain-Barre syndrome, polyarteritis nodosa, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis, sjogren syndrome, HIV infection, syphhilis infection, herpes infection, hepatitis infection, colorado tick fever infection, diptheria infection, leprosy, Lyme disease, and amyloidosis.

[0079] Examples of peripheral neuropathies caused by drugs include, but are not limited to neuropathy caused by amiodarone, hydralazine, perhexiline, chemotherapeutic drugs, vincristine, cisplatin, metronidazole (Flagyl), nitrofurantoin, thalidomide, INH (isoniazid) , Dapsone, anticonvulsants, Phenytoin, Disulfiram, zidovudine, retrovir, AZT, didanosine, (Videx), stavudine (Zerit), zalcitabine (Hivid), ritonavir (Norvir), amprenavir (Agenerase), lovastatin (Mevacor), indapamid (Lozol), gemfibrozil (Lopid)

[0080] Other miscellaneous causes or peripheral neuropathy include, but are not limited to ischemia, prolonged exposure to cold temperature, prolonged pressure on, or compression of a nerve, and trauma.

[0081] Peripheral neuropathies are characterized by damage to the either the sensory, motor, or autonomic peripheral nerves. The symptoms and effects of peripheral neuropathies depend on the types of nerves affected. Damage to such nerves can result in one or more of pain (neuropathic pain), loss of sensation, and loss of muscular control, abnormal blood pressure, abnormal heart function, digestion problems, and the like.

[0082] Damage to sensory fibers may result in changes in sensation, burning sensations, nerve pain (neuralgia, neuropathic pain), tingling, numbness, inability to determine joint position, and incoordination. Damage to the motor fibers may affect muscle control and can cause weakness, cramps, loss of muscle bulk, and loss of dexterity, paralysis, muscle atrophy, Muscle twitching (fasciculation), difficulty breathing or swallowing, falling. The autonomic nerves control involuntary and semi-voluntary functions, such as control of the internal organs, control of breathing, and blood pressure. Damage to autonomic nerves may cause, inability to regulate blood pressure, respiratory problems, problems of the digestive system (including nausea, vomiting, abdominal bloating, early satiety, diarrhea, constipation, unintentional weight loss), problems with the genitourinary system, (such as urinary incontinence, other bladder-function disorders, and male impotence.

[0083] Examples of specific nerves that may be affected in peripheral neuropathies include, but are not limited to, the axillary nerve, the brachial plexus, the peroneal nerve, the distal median nerve, the facial nerves palsy, the femoral nerves, the radial nerves, the sciatic nerve, the tibial nerves, and the ulnar nerves.

[0084] Examples of central neuropathies include, but are not limited to, vestibular neuropathies, optic neuropathies, optic nerve neuropathies, and retinal neuropathies. Other types of central neuropathy are known to those of skill in the art, and are encompassed by the present invention.

Seizures

[0085] The term "seizure" as used herein includes epileptic seizures and non-epileptic seizure. Epileptic seizures result from, temporary abnormal electrical activity in the brain.

They can manifest as an alterations tonic or chronic movements, convulsions, sudden and involuntary contraction of a group of muscles, involuntary changes in body movement or function, numbness, alterations in mental state, alterations in sensation, alterations in awareness, changes in behavior, temporary loss of memory, visual disturbances, and various other symptoms. Symptoms experienced by a person during a seizure depend on where in the brain the disturbance in electrical activity occurs.

[0086] There are various different types of seizures, all of which are within the scope of the present invention. For example, seizures may be epileptic or non-epileptic, as described below. Seizures may also be classified according to whether the source of the seizure within the brain is localized (partial or focal onset seizures) or distributed (generalized seizures). Partial seizures are further divided on the extent to which consciousness is affected. If consciousness is unaffected the seizure is referred to as a simple partial seizure. If consciousness is affected, the seizure is referred to as a complex partial seizure. A partial seizure may also spread within the brain - a process known as secondary generalization. Generalized seizures are divided according to the effect on the body but all involve loss of consciousness. These include absence, myoclonic, clonic, tonic, tonic-clonic, and atonic seizures. In the past, seizures have also been classified as "petit mal", "grand mal", "Jacksonian", "psychomotor", and "temporal-lobe" seizures.

[0087] Epilepsy is a chronic neurological condition characterized by recurrent unprovoked seizures. These seizures involve abnormal, rhythmic discharges of cortical neurons. Epilepsy may be symptomatic or idiopathic. Symptomatic epilepsies are caused by structural or metabolic abnormality in the brain, which may be the result of factors such as genetic disorders (such as tuberous sclerosis or ring chromosome 20 syndrome), stroke, head injury, bacterial or viral encephalitis, alcohol use. There are several syndromes that associated with epilepsy, including, but not limited to, infantile spasms (West syndrome), benign childhood epilepsy with centro-temporal spikes (or benign rolandic epilepsy), benign childhood epilepsy with occipital paroxysms, juvenile myoclonic epilepsy (JME), temporal lobe epilepsy, frontal lobe epilepsy, Lennox-Gastaut syndrome, occipital lobe epilepsy, and fetal alcohol spectrum disorder (FASD). Idiopathic seizures are those for which no specific cause has been identified.

[0088] Certain triggers or environmental factors or can lead to an increased likelihood of seizures in subjects with epilepsy. Examples of such triggers include, but are not limited to,

sleep, the transition between sleep and wakefulness, tiredness, illness, constipation, menstruation, stress, and alcohol consumption. It should also be noted that, even in epileptic subjects, seizures may be triggered by some of the same specific events that cause "provoked" seizures in non-epileptic subjects.

[0089] Non-epileptic seizures appear outwardly similar to epileptic seizures but do not involve abnormal, rhythmic discharges of cortical neurons. Non-epileptic seizures are typically provoked by either physiological or psychological conditions. Seizures caused by psychological conditions are referred to as "psychogenic" non-epileptic seizures.

[0090] Causes of non-epileptic or "provoked" seizures include, but are not limited to, head injury, intoxication with drugs, drug toxicity (for example aminophylline or local anaesthetic toxicity, drugs that lower the seizure threshold (such as tricyclic antidepressants), infection (such as encephalitis or meningitis), fever leading to febrile convulsions, metabolic disturbances such as hypoglycaemia or hypoxia, withdrawal from drugs (such as anticonvulsants, sedatives, alcohol, barbiturates, and benzodiazepines), brain tumors, other brain lesions, eclampsia during pregnancy, photosensitivity, flashing or flickering lights and electroconvulsive therapy (ECT). It should be noted that the above stimuli may also trigger epileptic seizures.

Cognitive Disorders

[0091] In another aspect, the present invention is directed to the treatment and prevention of cognitive disorders, and also to methods and compositions for improvement of cognitive function more generally, even in the absence of a specific cognitive disorder. For example, improvement of cognitive function to combat the normal cognitive decline associated with aging, or to enhance cognitive function for other reasons, is encompassed by the present invention.

[0092] The terms "cognitive function" and "cognitive process" as used herein, include the mental processes of attention, learning and memory, perception, language skills, problem solving skills, and other type of cognitive function known to those of skill in the art. The terms "cognitive disorder," "cognitive disease," and "cognitive condition," as used herein, refer to situations in which processes are disrupted or abnormal. The term "cognitive disorder," as used herein encompasses all of the cognitive disorders described below and also all other cognitive disorders known to those of skill in the art. Types of cognitive disorders

that are within the scope of the invention include, but are not limited to, dementias, delirium, amnesias, post-traumatic stress disorder and stress-induced cognitive dysfunction.

[0093] The term "dementia" as used herein refers to decline in cognitive function due to damage or disease in the brain or central nervous system beyond that which might be expected from normal aging. Dementias typically affect cognitive functions such as learning, memory, attention, language skills, and problem solving skills. Types and causes of dementia include, but are not limited to, chronic diseases such as cancer, Alzheimer's disease, vascular dementia (also known as multi-infarct dementia), Binswanger's disease, dementia with Lewy bodies (DLB), alcohol-induced persisting dementia, frontotemporal lobar degenerations (FTLD), Pick's disease, frontotemporal dementia (or frontal variant FTLD), semantic dementia (or temporal variant FTLD), progressive non-fluent aphasia, Creutzfeldt-Jakob disease, Huntington's disease, Parkinson's disease, and AIDS dementia complex.

[0094] Other types of cognitive disorders that may be treated with the methods and compositions of the present invention include the various attention disorders. Attention-Deficit/Hyperactivity Disorder (ADHD; ADH is also referred to Attention-deficit syndrome (ADS)) is a neurological disorder initially appearing in childhood which manifests itself with symptoms such as hyperactivity, forgetfulness, poor impulse control, and distractibility. In neurological terms, ADHD is currently considered to be a persistent and chronic syndrome for which no medical cure is available. ADHD is believed to affect between 3-5% of the United States population, including both children and adults. ADH D is sometimes referred to as ADD when only inattentiveness and distractibility are problematic. ADHD can be classified into three subtypes: predominantly inattentive (sometimes referred to as ADD), predominantly hyperactive-impulsive, and combined. Those presenting impairing symptoms of ADHD who do not fully fit the criteria for any of the three subtypes can be diagnosed with "ADHD Not Otherwise Specified." The symptoms of ADHD are given the name "Hyperkinetic disorders". When a conduct disorder is present, the condition is referred to as "Hyperkinetic conduct disorder". All of the above conditions are within the scope of the present invention.

[0095] In one embodiment, the cogntive disorder is not Alzheimer's Disease. In another embodiment, the cogntive disorder is not memory loss. In another embodiment, the cogntive disorder is not age-dependent memory loss.

Prevention and Treatment

[0096] In one embodiment, the present invention provides compositions and methods that are useful for treating and/or preventing conditions affecting the nervous system, such as neuropathies, seizures and cognitive disorders.

[0097] In certain embodiments, the compositions and methods of the present invention may be used preventively in subjects who are not yet suffering from neuropathies, seizures or cognitive disorders, but whom exhibit one or more "risk factors" or are otherwise predisposed to the development of neuropathies, seizures or cognitive disorders.

Subjects

[0098] In preferred embodiments, the compositions described herein are administered therapeutically or prophylactically to subjects who are suffering from, or at risk of developing a disease, disorder or condition affecting the nervous system, such as a neuropathy, seizures or a cognitive disorder. Such a subject may be any animal. For example, in one embodiment, the subject is a mammal. Examples of mammals that may be treated using the methods and compositions of the invention include, but are not limited to, primates, rodents, ovine species, bovine species, porcine species, equine species, feline species and canine species. In preferred embodiments the subjects are human.

[0099] In preferred embodiments, the methods and compositions of the invention may be used to treat or prevent a disease, disorder or condition affecting the nervous system, such as a neuropathy, seizures or a cognitive disorder, in a subject having a mutation in a ryanodine receptor gene, such as a mutation that results in defective functioning of the ryanodine receptor, such as an increased open probability or "leakiness" of the ryanodine receptor.

[00100] In other embodiments, the "subjects" of the present invention may also be *in vitro* or *in vivo* systems, including, without limitation, isolated or cultured cells or tissues, *in vitro* assay systems.

Compositions

[00101] The compounds of the invention may be formulated into compositions for administration to subjects for the treatment and/or prevention of a disease, disorder or condition affecting the nervous system, such as a neuropathy, seizures or a cognitive disorder.

The compositions of the present invention comprise one or more of the 1,4, benzothiazepine compounds described herein (such as the compounds of Formula I, I-a, I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-i, I-j, I-k, I-l, I-m, I-n, I-o, I-p, or Formula II), in admixture with a pharmaceutically acceptable diluents and/or carrier and optionally one or more other pharmaceutically acceptable additives. The pharmaceutically-acceptable diluents and/or carriers and any other additives must be "acceptable" in the sense of being compatible with the other ingredients of the composition and not deleterious to the subject to whom the composition will be administered. One of skill in the art can readily formulate the compounds of the invention into compositions suitable for administration to subjects, such as human subjects, for example using the teaching a standard text such as Remington's Pharmaceutical Sciences, 18th ed, (Mack Publishing Company: Easton, Pa., 1990), pp. 1635-36), and by taking into account the selected route of delivery.

[00102] Examples of diluents and/or carriers and/or other additives that may be included in the compositions of the invention include, but are not limited to, water, glycols, oils, alcohols, aqueous solvents, organic solvents, DMSO, saline solutions, physiological buffer solutions, peptide carriers, starches, sugars, preservatives, antioxidants, coloring agents, pH buffering agents, granulating agents, lubricants, binders, disintegrating agents, emulsifiers, binders, excipients, extenders, glidants, solubilizers, stabilizers, surface active agents, suspending agents, tonicity agents, viscosity-altering agents, carboxymethyl cellulose, crystalline cellulose, glycerin, gum arabic, lactose, magnesium stearate, methyl cellulose, powders, saline, sodium alginate. The combination of diluents and/or carriers and/or other additives used can be varied taking into account the nature of the active agents used (for example the solubility and stability of the active agents), the route of delivery (e.g. oral, parenteral, etc.), whether the agents are to be delivered over an extended period (such as from a controlled-release capsule), whether the agents are to be co-administered with other agents, and various other factors. One of skill in the art will readily be able to formulate the compounds for the desired use without undue experimentation.

Dosing & Administration

[00103] In accordance with a method of the present invention, the compounds of Formula I, I-a, I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-i, I-j, I-k, I-l, I-m, I-n, I-o, I-p, or Formula II, may be administered to the subject (or contacted with cells of the subject) in an amount effective to treat or prevent a disease, disorder or condition affecting the nervous system,

such as a neuropathy, seizures, or a cognitive disorder, and/or in an amount effective to reduce calcium "leak" through the RyR channel, and/or in an amount effective to reduce the calcium current through the RyR channel, and/or in an amount effective to stabilize gating of the RyR channel, and/or in amount effective to increase the binding of calstabin to the RyR complex in the subject, and/or in amount effective to reverse a malfunction of a RyR channel in the subject, particularly in the cardiac cells of the subject.

[00104] One of skill in the art can readily determine what would be an effective amount of the agents of the invention to be administered to a subject, taking into account whether the agent is being used prophylactically or therapeutically, and taking into account other factors such as the age, weight and sex of the subject, any other drugs that the subject may be taking, any allergies or contraindications that the subject may have, and the like. For example, an effective amount can be determined by the skilled artisan using known procedures, including analysis of titration curves established *in vitro* or *in vivo*. Also, where the desired subject is a human, one of skill in the art can determine the effective dose from performing pilot experiments in suitable animal model species and scaling the doses up or down depending on the subjects weight etc. Effective amounts can also be determined by performing clinical trials in individuals of the same species as the subject, for example starting at a low dose and gradually increasing the dose and monitoring the effects on cardiac hypertrophy. Appropriate dosing regimens can also be determined by one of skill in the art without undue experimentation, in order to determine, for example, whether to administer the agent in one single dose or in multiple doses, and in the case of multiple doses, to determine an effective interval between doses.

[00105] In one embodiment, an effective amount of the compounds of the invention to administer to a subject ranges from about 0.01 mg/kg/day to about 20 mg/kg/day, and/or is an amount sufficient to achieve plasma levels ranging from about 300 ng/ml to about 1000 ng/ml. In one embodiment, the amount of compounds from the invention ranges from about 5 mg/kg/day to about 20 mg/kg/day. In another embodiment, from about 10 mg/kg/day to about 20 mg/kg/day is administered. In another embodiment, from about 0.01 mg/kg/day to about 10 mg/kg/day is administered. In another embodiment, from about 0.01 mg/kg/day to about 5 mg/kg/day is administered. In another embodiment, from about 0.05 mg/kg/day to about 5 mg/kg/day is administered. In another, preferred embodiment, from about 0.05 mg/kg/day to about 1 mg/kg/day is administered.

[00106] The compositions described herein may be administered to a subject by any suitable method that allows the agent to exert its effect on the subject *in vivo*. For example, the compositions may be administered to the subject by known procedures including, but not limited to, by oral administration, sublingual or buccal administration, parenteral administration, transdermal administration, via inhalation, via nasal delivery, vaginally, rectally, and intramuscularly. The compounds of the invention may be administered parenterally, or by epifascial, intracapsular, intracutaneous, subcutaneous, intradermal, intrathecal, intramuscular, intraperitoneal, intrasternal, intravascular, intravenous, parenchymatous, or sublingual delivery. Delivery may be by injection, infusion, catheter delivery, or some other means, such as by tablet or spray.

[00107] For oral administration, a formulation of the compounds of the invention may be presented as capsules, tablets, powders, granules, or as a suspension or solution. The formulation may contain conventional additives, such as lactose, mannitol, cornstarch or potato starch, binders, crystalline cellulose, cellulose derivatives, acacia, cornstarch, gelatins, disintegrators, potato starch, sodium carboxymethylcellulose, dibasic calcium phosphate, anhydrous or sodium starch glycolate, lubricants, and/or or magnesium stearate.

[00108] For parenteral administration (*i.e.*, administration by through a route other than the alimentary canal), the compounds of the invention may be combined with a sterile aqueous solution that is isotonic with the blood of the subject. Such a formulation may be prepared by dissolving the active ingredient in water containing physiologically-compatible substances, such as sodium chloride, glycine and the like, and having a buffered pH compatible with physiological conditions, so as to produce an aqueous solution, then rendering the solution sterile. The formulation may be presented in unit or multi-dose containers, such as sealed ampoules or vials. The formulation may be delivered by injection, infusion, or other means known in the art.

[00109] For transdermal administration, the compounds of the invention may be combined with skin penetration enhancers, such as propylene glycol, polyethylene glycol, isopropanol, ethanol, oleic acid, *N*-methylpyrrolidone and the like, which increase the permeability of the skin to the compounds of the invention and permit the compounds to penetrate through the skin and into the bloodstream. The compositions also may be further combined with a polymeric substance, such as ethylcellulose, hydroxypropyl cellulose, ethylene/vinylacetate, polyvinyl pyrrolidone, and the like, to provide the composition in gel

form, which are dissolved in a solvent, such as methylene chloride, evaporated to the desired viscosity and then applied to backing material to provide a patch.

[00110] In some embodiments, the composition is in unit dose form such as a tablet, capsule or single-dose injection or infusion vial.

[00111] In certain embodiments, the agents described herein may be used in combination with other agents useful for the treatment of neuropathies, seizures or cognitive disorders or with other agents that ameliorate the effect of certain risk factors for neuropathies, seizures or cognitive disorders. For example, in one embodiment, the agents of the invention may be delivered to a subject as part of a composition containing one or more additional active agents. In another embodiment, the agents of the invention may be delivered to a subject in a composition or formulation containing only that active agent, while one or more other agents useful for the treatment of neuropathies, seizures or cognitive disorders may be also be administered to the subject in one or more separate compositions or formulations.

[00112] The agents of the invention and the other agents useful for the treatment of neuropathies, seizures or cognitive disorders may be administered to the subject at the same time, or at different times. For example, the agents of the invention and the other agents may be administered within minutes, hours, days, weeks, or months of each other, for example as part of the overall treatment regimen of a subject.

[00113] The agents of the invention may also be used in combination with surgical or other interventional treatment regimens used for the treatment of a disease, disorder or condition affecting the nervous system, such as a neuropathy, seizures or a cognitive disorder.

Screening for new compounds useful for treating neuropathies, seizures or cognitive disorders

[00114] In another embodiment, the present invention is directed to methods for identifying additional compounds that may be useful for the treatment of neuropathies, seizures or cognitive disorders. Such methods may be based on, *inter alia*, identifying compounds that increase binding of calstabins to RyRs, and/or decrease the calcium current through RyR channels, and the like. Examples of suitable assays and screening methods that may be used to identify new compounds that may be useful for the treatment of neuropathies,

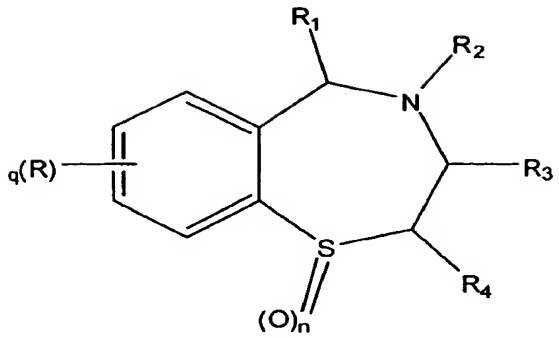
seizures or cognitive disorders are described in U.S. patent applications 09/568,474, 10/288,606, 10/680,988, 10/608,723, 10/809,089, 10/763,498, 10/794,218, 11/088,058, 11/088,123, 11/212,309, 11/506,285, and 11/212,413, the contents of which are hereby incorporated by reference.

Compounds

[00115] The present invention encompasses, *inter alia*, the use of the compounds described herein for the treatment and/or prevention of a disease, disorder or condition affecting the nervous system, such as a neuropathy, seizures or a cognitive disorder, methods of treatment and/or prevention comprising administration of such compounds to subjects in need thereof, and compositions containing such compounds for use in the treatment and/or prevention of a disease, disorder or condition affecting the nervous system, such as a neuropathy, seizures or a cognitive disorder. The compounds of the invention decrease the open probability of RyR receptor channels, particularly PKA phosphorylated RyR channels, and thereby decrease the Ca^{2+} current through such channels. The compounds of the invention exert this effect, at least in part, by increasing the affinity with which calstabin proteins bind to RyRs, and/or by inhibiting a decrease in binding of calstabins to RyRs, and/or by inhibiting dissociation of calstabins from RyRs, particularly PKA phosphorylated RyRs. The compounds of the invention decrease the open probability of RyR channels and decrease the "leak" of Ca^{2+} through such channels. In addition to regulating Ca^{2+} levels in cells, the compounds of the invention modulate the Na^{+} current and the inward-rectifier K^{+} current in cells.

[00116] Representative embodiments of the compounds of the invention are 1,4, benzothiazepine compounds such as JTV-519 or K-201, or any of the compounds of formulae I, I-a, I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-i, I-j, I-k, I-l, I-m, I-n, I-o, I-p, or Formula II, as described below.

[00117] The structure of Formula I is as follows:



wherein,

n is 0, 1, or 2;

q is 0, 1, 2, 3, or 4;

each R is independently selected from the group consisting of H, halogen, -OH, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-SO_3H$, $-S(=O)_2$alkyl, -S(=O)alkyl, $-OS(=O)_2CF_3$, acyl, -O-acyl, alkyl, alkoxyl, alkylamino, alkylarylamino, alkylthio, cycloalkyl, alkylaryl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino; wherein each acyl, -O-acyl, alkyl, alkoxyl, alkylamino, alkylarylamino, alkylthio, cycloalkyl, alkylaryl, aryl, heteroaryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino may be optionally substituted;

R_1 is selected from the group consisting of H, oxo, alkyl, alkenyl, aryl, alkylaryl, cycloalkyl, heteroaryl, and heterocyclyl; wherein each alkyl, alkenyl, aryl, alkylaryl, cycloalkyl, heteroaryl, and heterocyclyl may be optionally substituted;

R_2 is selected from the group consisting of H, $-C(=O)R_5$, $-C(=S)R_6$, $-SO_2R_7$, $-P(=O)R_8R_9$, $-(CH_2)_m-R_{10}$, alkyl, aryl, alkylaryl, heteroaryl, cycloalkyl, cycloalkylalkyl, and heterocyclyl; wherein each alkyl, aryl, alkylaryl, heteroaryl, cycloalkyl, cycloalkylalkyl, and heterocyclyl may be optionally substituted, and wherein m is 0, 1, 2, 3, or 4;

R_3 is selected from the group consisting of H , $-CO_2Y$, -C(=O)NHY, acyl, -O-acyl, alkyl, alkenyl, aryl, alkylaryl, cycloalkyl, heteroaryl, and heterocyclyl; wherein each acyl, alkyl, alkenyl, aryl, alkylaryl, cycloalkyl, heteroaryl, and heterocyclyl may be optionally substituted; and wherein Y is selected from the group consisting of H, alkyl, aryl, alkylaryl, cycloalkyl, heteroaryl, and heterocyclyl, and wherein each alkyl, aryl, alkylaryl, cycloalkyl, heteroaryl, and heterocyclyl may be optionally substituted;

R_4 is selected from the group consisting of H, alkyl, alkenyl, aryl, alkylaryl, cycloalkyl, heteroaryl, and heterocyclyl; wherein each alkyl, alkenyl, aryl, alkylaryl, cycloalkyl, heteroaryl, and heterocyclyl may be optionally substituted;

R_5 is selected from the group consisting of $-NR_{15}R_{16}$, $-(CH_2)_zNR_{15}R_{16}$, $-NHNR_{15}R_{16}$, -NHOH, $-OR_{15}$, $-C(=O)NHNR_{15}R_{16}$, $-CO_2R_{15}$, $-C(=O)NR_{15}R_{16}$, $-CH_2X$, acyl, alkyl, alkenyl, aryl, alkylaryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkyl, alkenyl, aryl, alkylaryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, and heterocyclylalkyl may be optionally substituted, and wherein z is 1, 2, 3, 4, 5, or 6;

R_6 is selected from the group consisting of $-OR_{15}$, $-NHNR_{15}R_{16}$, -NHOH, $-NR_{15}R_{16}$, $-CH_2X$, acyl, alkenyl, alkyl, aryl, alkylaryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkenyl, alkyl, aryl, alkylaryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, and heterocyclylalkyl may be optionally substituted;

R_7 is selected from the group consisting of $-OR_{15}$, $-NR_{15}R_{16}$, $-NHNR_{15}R_{16}$, -NHOH, $-CH_2X$, alkyl, alkenyl, alkynyl, aryl, alkylaryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, and heterocyclylalkyl; wherein each alkyl, alkenyl, alkynyl, aryl, alkylaryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, and heterocyclylalkyl may be optionally substituted;

R_8 and R_9 independently are selected from the group consisting of OH, acyl, alkenyl, alkoxyl, alkyl, alkylamino, aryl, alkylaryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkenyl, alkoxyl, alkyl, alkylamino, aryl, alkylaryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, and heterocyclylalkyl may be optionally substituted;

R_{10} is selected from the group consisting of $-NR_{15}R_{16}$, OH, $-SO_2R_{11}$, $-NHSO_2R_{11}$, $C(=O)(R_{12})$, $NHC=O(R_{12})$, $-OC=O(R_{12})$, and $-P(=O)R_{13}R_{14}$;

R_{11}, R_{12}, R_{13}, and R_{14} independently are selected from the group consisting of H, OH, NH_2, $-NHNH_2$, -NHOH, acyl, alkenyl, alkoxyl, alkyl, alkylamino, aryl, alkylaryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkenyl, alkoxyl, alkyl, alkylamino, aryl, alkylaryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, and heterocyclylalkyl may be optionally substituted;

X is selected from the group consisting of halogen, -CN, $-CO_2R_{15}$, $-C(=O)NR_{15}R_{16}$, $-NR_{15}R_{16}$, $-OR_{15}$, $-SO_2R_7$, and $-P(=O)R_8R_9$; and

R_{15} and R_{16} independently are selected from the group consisting of H, acyl, alkenyl, alkoxyl, OH, NH_2, alkyl, alkylamino, aryl, alkylaryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkenyl, alkoxyl, alkyl, alkylamino, aryl, alkylaryl, cycloalkyl, cycloalkylalkyl, heteroaryl, heterocyclyl, and heterocyclylalkyl may be optionally substituted; and optionally R_{15} and R_{16} together with the N to which they are bonded may form a heterocycle which may be substituted;

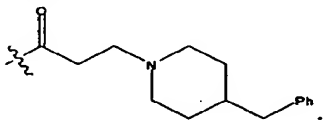
the nitrogen in the benzothiazepine ring may optionally be a quaternary nitrogen; and

enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, or prodrugs thereof.

[00118] In certain embodiments, the present invention uses compounds of Formula I, with the proviso that when q is 0 and n is 0, then R_2 is not H, Et, $-C(=O)NH_2$, (=O)NHPh, -C(=S)NH-nButyl, $-C(=O)NHC(=O)CH_2Cl$, -C(=O)H, -C(=O)Me, -C(=O)Et, $-C(=O)CH=CH_2$, $-S(=O)_2Me$, or $-S(=O)_2Et$;

further provided that when q is 0 and n is 1 or 2, then R_2 is not -C(=O)Me, -C(=O)Et, $-S(=O)_2Me$, or $-S(=O)_2Et$;

further provided that when q is 1, and R is Me, Cl, or F at the 6 position of the benzothiazepene ring, then R_2 is not H, Me, -C(=O)H, -C(=O)Me, -C(=O)Et, -C(=O)Ph, $-S(=O)_2Me$, or $-S(=O)_2Et$; and

further provided that when q is 1, n is 0, and R is OCT_3, OH, C_1-C_3 alkoxyl at the 7 position of the benzothiazepene ring, then R_2 is not H, $-C(=O)CH=CH_2$, or  .

[00119] In one embodiment of the present invention, for compounds of Formula I, if R_2 is $C=O(R_5)$ or SO_2R_7, then R is at positions 2, 3, or 5 on the benzene ring.

[00120] In another embodiment of the invention, for compounds of Formula I, if R_2 is $C=O(R_5)$ or SO_2R_7, then each R is independently selected from the group consisting of H, halogen, -OH, $-NH_2$, $-NO_2$, -CN, $-N_3$, $-SO_3H$, acyl, alkyl, alkylamino, cycloalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino; wherein each acyl, alkyl, alkoxyl, alkylamino, cycloalkyl, heterocyclyl,

heterocyclylalkyl, alkenyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino may be substituted with one or more radicals independently selected from the group consisting of halogen, N, O, -S-, -CN, $-N_3$, -SH, nitro, oxo, acyl, alkyl, alkoxyl, alkylamino, alkenyl, aryl, (hetero-)cycloalkyl, and (hetero-)cyclyl.

[00121] In another embodiment of the invention, for compounds of Formula I, if R_2 is $C{=}O(R_5)$ or SO_2R_7, then there are at least two R groups attached to the benzene ring. Furthermore, there are at least two R groups attached to the benzene ring, and both R groups are attached at positions 2, 3, or 5 on the benzene ring. Still furthermore, each R is independently selected from the group consisting of H, halogen, -OH, $-NH_2$, $-NO_2$, -CN, $-N_3$, $-SO_3H$, acyl, alkyl, alkylamino, cycloalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino; wherein each acyl, alkyl, alkoxyl, alkylamino, cycloalkyl, heterocyclyl, heterocyclylalkyl, alkenyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino may be substituted with one or more radicals independently selected from the group consisting of halogen, N, O, -S-, -CN, $-N_3$, -SH, nitro, oxo, acyl, alkyl, alkoxyl, alkylamino, alkenyl, aryl, (hetero-)cycloalkyl, and (hetero-)cyclyl.

[00122] In another embodiment of the invention, for compounds of Formula I, if R_2 is $C{=}O(R_5)$, then R_5 is selected from the group consisting of $-NR_{16}$, $-(CH_2)_zNR_{15}R_{16}$, $NHNHR_{16}$, NHOH, $-OR_{15}$, $CONH_2NHR_{16}$, $CONR_{16}$, CH_2X, acyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted with one or more radicals independently selected from the group consisting of halogen, N, O, -S-, -CN, $-N_3$, nitro, oxo, acyl, alkyl, alkoxyl, alkylamino, alkenyl, aryl, (hetero-)cycloalkyl, and (hetero-)cyclyl.

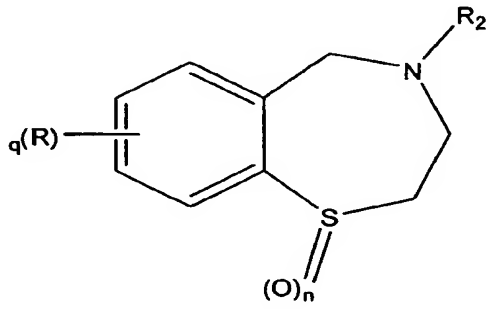
[00123] In another embodiment, the present invention uses compounds of Formula I, as described above, with the proviso that the compound is not S4, S7, S20, S24, S25, S26, S27, or S36.

[00124] In another embodiment, the present invention uses compounds of Formula I, as described above, with the proviso that the compound is not S1, S2, S3, S4, S5, S6, S7, S9, S11, S12, S13, S14, S19, S20, S22, S23, S24, S25, S26, S27, S36, S37, S38, S40, S43, S44, S45, S46, S47, S48, S49, S50, S51, S52, S53, S54, S55, S56, S57, S58, S59, S60, S61, S62, S63, S64, S66, S67, S68, S69, S70, S71, S72, S73, S74, S75, S76, S77, S78, S79, S80, S81,

S82, S83, S84, S85, S86, S87, S88, S89, S90, S91, S92, S93, S94, S95, S96, S97, S98, S99, or S100.

[00125] In another embodiment, the present invention uses 1,4, benzothiazepine compounds, such as compounds of Formula I, with the proviso that the compound is not JTV-519.

[00126] In one embodiment, the present invention provides methods and uses which comprise administering compounds of Formula **I-a:**



(I-a)

wherein:

n is 0, 1, or 2;

q is 0, 1, 2, 3, or 4;

each R is independently selected from the group consisting of H, halogen, -OH, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-SO_3H$, $-S(=O)_2$alkyl, -S(=O)alkyl, $-OS(=O)_2CF_3$, acyl, alkyl, alkoxyl, alkylamino, alkylthio, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino; wherein each acyl, alkyl, alkoxyl, alkylamino, alkylthio, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino may be substituted or unsubstituted;

R_2 is selected from the group consisting of H, $-C=O(R_5)$, $-C=S(R_6)$, $-SO_2R_7$, $-P(=O)R_8R_9$, $-(CH_2)_m-R_{10}$, alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, and heterocyclyl; wherein each alkyl, aryl, heteroaryl, cycloalkyl, cycloalkylalkyl, and heterocyclyl may be substituted or unsubstituted, wherein m is 0, 1, 2, 3, or 4;

R_5 is selected from the group consisting of $-NR_{15}R_{16}$, $-(CH_2)_zNR_{15}R_{16}$, $-NHNR_{15}R_{16}$, -NHOH, $-OR_{15}$, $-C(=O)NHNR_{15}R_{16}$, $-CO_2R_{15}$, $-C(=O)NR_{15}R_{16}$, $-CH_2X$, acyl, alkyl, alkenyl, alkynyl,

aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkyl, alkenyl, alkynyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted, and wherein z is 1, 2, 3, 4, 5, or 6;

R_6 is selected from the group consisting of $-OR_{15}$, $-NHNR_{15}R_{16}$, -NHOH, $-NR_{15}R_{16}$, $-CH_2X$, acyl, alkenyl, alkyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkenyl, alkyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted;

R_7 is selected from the group consisting of H, $-OR_{15}$, $-NR_{15}R_{16}$, $-NHNR_{15}R_{16}$, -NHOH, $-CH_2X$, alkyl, akenyl, alkynyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each alkyl, akenyl, alkynyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted;

R_8 and R_9 independently are selected from the group consisting of -OH, acyl, alkenyl, alkoxyl, alkyl, alkylamino, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkenyl, alkoxyl, alkyl, alkylamino, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted;

R_{10} is selected from the group consisting of $-NR_{15}R_{16}$, OH, $-SO_2R_{11}$, $-NHSO_2R_{11}$, $-C(=O)R_{12}$, $-NH(C=O)R_{12}$, $-O(C=O)R_{12}$, and $-P(=O)R_{13}R_{14}$;

R_{11}, R_{12}, R_{13}, and R_{14} independently are selected from the group consisting of H, OH, NH_2, $-NHNH_2$, -NHOH, acyl, alkenyl, alkoxyl, alkyl, alkylamino, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkenyl, alkoxyl, alkyl, alkylamino, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted;

X is selected from the group consisting of halogen, -CN, $-CO_2R_{15}$, $-C(=O)NR_{15}R_{16}$, $-NR_{15}R_{16}$, $-OR_{15}$, $-SO_2R_7$, and $-P(=O)R_8R_9$; and

R_{15} and R_{16} independently are selected from the group consisting of H, acyl, alkenyl, alkoxyl, OH, NH_2, alkyl, alkylamino, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkenyl, alkoxyl, alkyl, alkylamino, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted; and optionally R_{15} and R_{16} together with the N to which they are bonded may form a heterocycle which may be substituted or unsubstituted;

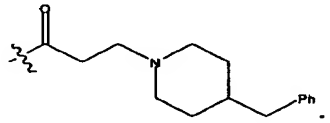
the nitrogen in the benzothiazepine ring may be optionally a quaternary nitrogen; and

enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and prodrugs thereof.

[00127] In one embodiment, it is provided that when q is 0 and n is 0, then R_2 is not H, Et, $-C(=O)NH_2$, $(=O)NHPh$, $-C(=S)NH$-nButyl, $-C(=O)NHC(=O)CH_2Cl$, $-C(=O)H$, $-C(=O)Me$, $-C(=O)Et$, $-C(=O)CH=CH_2$, $-S(=O)_2Me$, or $-S(=O)_2Et$;

further provided that when q is 0 and n is 1 or 2, then R_2 is not $-C(=O)Me$, $-C(=O)Et$, $-S(=O)_2Me$, or $-S(=O)_2Et$;

further provided that when q is 1, and R is Me, Cl, or F at the 6 position of the benzothiazepene ring, then R_2 is not H, Me, $-C(=O)H$, $-C(=O)Me$, $-C(=O)Et$, $-C(=O)Ph$, $-S(=O)_2Me$, or $-S(=O)_2Et$; and

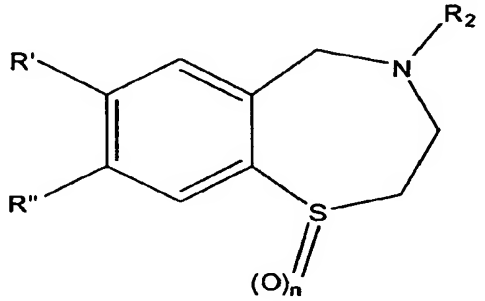
further provided that when q is 1, n is 0, and R is OCT_3, OH, C_1-C_3 alkoxyl at the 7 position of the benzothiazepene ring, then R_2 is not H, $-C(=O)CH=CH_2$, or 

.

[00128] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-a**, wherein each R is independently selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$, Ph, $-NHCH_2Ph$, $-C(=O)Me$, $-OC(=O)Me$, morpholinyl and propenyl; and n is 0, 1, or 2.

[00129] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-a**, wherein R_2 is selected from the group consisting of $-C=O(R_5)$, $-C=S(R_6)$, $-SO_2R_7$, $-P(=O)R_8R_9$, and $-(CH_2)_m$-R_{10}.

[00130] In yet another embodiment, the present invention provides methods and uses which comprise administering compounds of formula **I-b**:



(I-b)

wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-SO_3H$, $-S(=O)_2$alkyl, -S(=O)alkyl, $-OS(=O)_2CF_3$, acyl, alkyl, alkoxyl, alkylamino, alkylthio, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino; and wherein each acyl, alkyl, alkoxyl, alkylamino, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio may be substituted or unsubstituted;

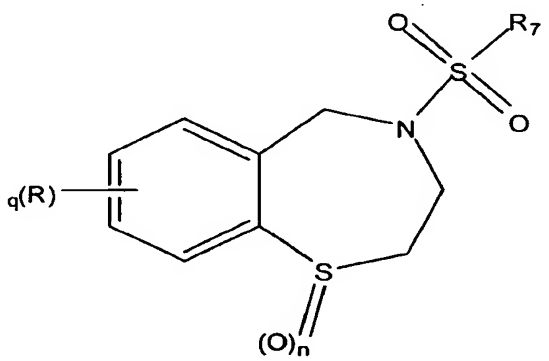
R_2 and n are as defined in compounds of formula **I-a** above;

and enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and pro-drugs thereof.

[00131] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-b**, wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$, Ph, $-NHCH_2Ph$, -C(=O)Me, -OC(=O)Me, morpholinyl and propenyl; and n is 0, 1 or 3. In some cases, R' is H or OMe, and R" is H.

[00132] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-b**, wherein R_2 is selected from the group consisting of $-C=O(R_5)$, $-C=S(R_6)$, $-SO_2R_7$, $-P(=O)R_8R_9$, and $-(CH_2)_m-R_{10}$.

[00133] In yet another embodiment, the present invention provides methods and uses which comprise administering compounds formula of **I-c**:



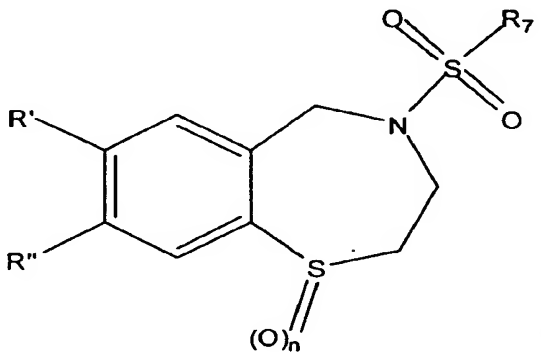
(I-c)

wherein each R, R_7, q, and n is as defined in compounds of formula **I-a** above; and enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and pro-drugs thereof.

[00134] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-c**, wherein each R is independently selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$, Ph, $-NHCH_2Ph$, -C(=O)Me, -OC(=O)Me, morpholinyl and propenyl; and n is 0, 1, or 2.

[00135] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-c**, wherein R_7 is selected from the group consisting of -OH, $-NR_{15}R_{16}$, alkyl, alkenyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each alkyl, akenyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted.

[00136] In a further embodiment, the present invention provides methods and uses which comprise administering compounds of formula of **I-d:**



(I-d)

wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-SO_3H$, $-S(=O)_2$alkyl, -S(=O)alkyl, $-OS(=O)_2CF_3$, acyl, alkyl, alkoxyl, alkylamino, alkylthio, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino; and wherein each acyl, alkyl, alkoxyl, alkylamino, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio may be substituted or unsubstituted;

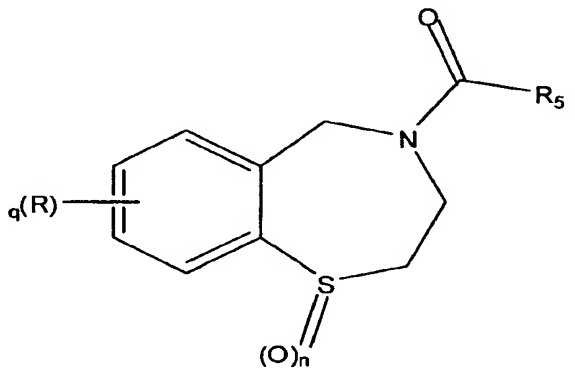
R_7 and n are as defined in compounds of formula **I-a** above; and enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and pro-drugs thereof.

[00137] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-d**, wherein R' and R" are

independently selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$, Ph, $-NHCH_2Ph$, -C(=O)Me, -OC(=O)Me, morpholinyl and propenyl; and n is 0, 1 or 3. In some cases, R' is H or OMe, and R" is H.

[00138] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-d**, wherein R_7 is selected from the group consisting of -OH, $-NR_{15}R_{16}$, alkyl, alkenyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each alkyl, akenyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted.

[00139] In one embodiment, the present invention provides methods and uses which comprise administering compounds of formula of **I-e**:



(I-e)

wherein each R, R_5, q and n is as defined compounds of formula **I-a** above; and enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and pro-drugs thereof.

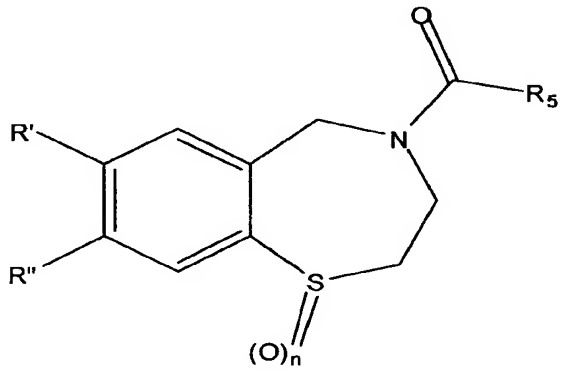
[00140] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-c**, wherein each R is independently selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$, Ph, $-NHCH_2Ph$, -C(=O)Me, -OC(=O)Me, morpholinyl and propenyl; and n is 0, 1, or 2.

[00141] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-e**, wherein R_5 is selected from the group consisting of $-NR_{15}R_{16}$, $-(CH_2)_zNR_{15}R_{16}$, -NHOH, $-OR_{15}$, $-CH_2X$, alkyl, alkenyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkyl,

alkenyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted.

[00142] In some embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-e**, wherein R_5 is an alkyl substituted by at least one labeling group, such as a fluorescent, a bioluminescent, a chemiluminescent, a colorimetric and a radioactive labeling group. A fluorescent labeling group can be selected from bodipy, dansyl, fluorescein, rhodamine, Texas red, cyanine dyes, pyrene, coumarins, Cascade Blue™, Pacific Blue, Marina Blue, Oregon Green, 4',6-Diamidino-2-phenylindole (DAPI), indopyra dyes, lucifer yellow, propidium iodide, porphyrins, arginine, and variants and derivatives thereof.

[00143] In another embodiment, the present invention provides methods and uses which comprise administering compounds of formula of **I-f**:



(I-f)

wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-SO_3H$, $-S(=O)_2$alkyl, -S(=O)alkyl, $-OS(=O)_2CF_3$, acyl, alkyl, alkoxyl, alkylamino, alkylthio, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino; and wherein each acyl, alkyl, alkoxyl, alkylamino, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio may be substituted or unsubstituted;

R_5 and n are as defined in compounds of formula **I-a** above;

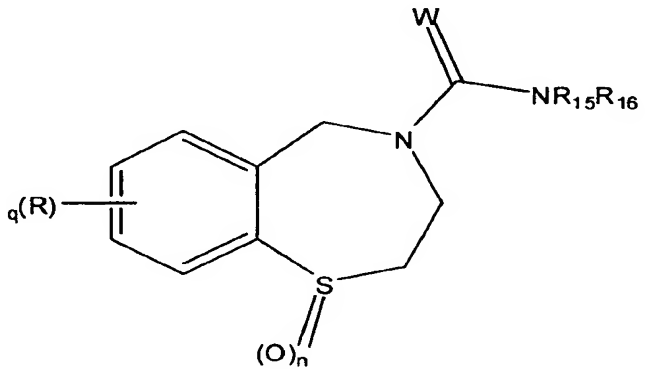
and enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and pro-drugs thereof.

[00144] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-f**, wherein R' and R" are

independently selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$, Ph, $-NHCH_2Ph$, -C(=O)Me, -OC(=O)Me, morpholinyl and propenyl; and n is 0, 1 or 3. In some cases, R' is H or OMe, and R" is H.

[00145] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-f**, wherein $-(CH_2)_zNR_{15}R_{16}$, selected from the group consisting of $-NR_{15}R_{16}$, -NHOH, $-OR_{15}$, $-CH_2X$, alkyl, alkenyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkyl, alkenyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted.

[00146] In yet another embodiment, the present invention provides methods and uses which comprise administering compounds of formula of **I-g**:



(I-g)

wherein W is S or O; each R, R_{15}, R_{16}, q, and n is as defined in compounds of formula **I-a** above; and enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and pro-drugs thereof.

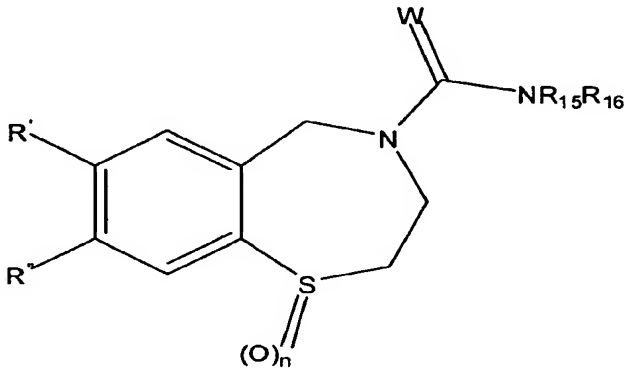
[00147] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-g**, wherein each R is independently selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$, Ph, $-NHCH_2Ph$, -C(=O)Me, -OC(=O)Me, morpholinyl and propenyl; and n is 0, 1, or 2.

[00148] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-g**, wherein R_{15} and R_{16} independently are selected from the group consisting of H, OH, NH_2, alkyl, alkylamino, aryl, cycloalkyl,

cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each alkyl, alkylamino, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted; and optionally R_{15} and R_{16} together with the N to which they are bonded may form a heterocycle which may be substituted.

[00149] In some embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-g**, wherein W is O or S.

[00150] In yet another embodiment, the present invention provides methods and uses which comprise administering compounds of formula of **I-h**:



(I-h)

wherein W is S or O;

wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-SO_3H$, $-S(=O)_2$alkyl, -S(=O)alkyl, $-OS(=O)_2CF_3$, acyl, alkyl, alkoxyl, alkylamino, alkylthio, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino; and wherein each acyl, alkyl, alkoxyl, alkylamino, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio may be substituted or unsubstituted;

R_{15}, R_{16} and n are as defined in compounds of formula **I-a** above;

and enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and pro-drugs thereof.

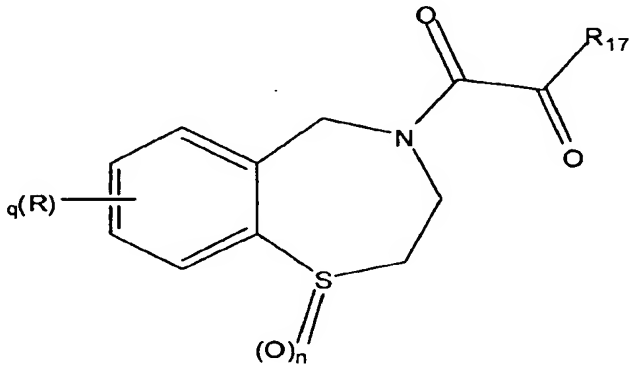
[00151] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-h**, wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$,

Ph, -NHCH$_2$Ph, -C(=O)Me, -OC(=O)Me, morpholinyl and propenyl; and n is 0, 1 or 3. In some cases, R' is H or OMe, and R" is H.

[00152] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-h**, wherein R_{15} and R_{16} independently are selected from the group consisting of H, OH, NH_2, alkyl, alkylamino, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each alkyl, alkylamino, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted; and optionally R_{15} and R_{16} together with the N to which they are bonded may form a heterocycle which may be substituted.

[00153] In some embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-g**, wherein W is O or S.

[00154] In a further embodiment, the present invention provides methods and uses which comprise administering compounds of formula of **I-i**:



(I-i)

wherein R_{17} is selected from the group consisting of $-NR_{15}R_{16}$, $-NHNR_{15}R_{16}$, -NHOH, $-OR_{15}$, $-CH_2X$, alkenyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each alkenyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted;

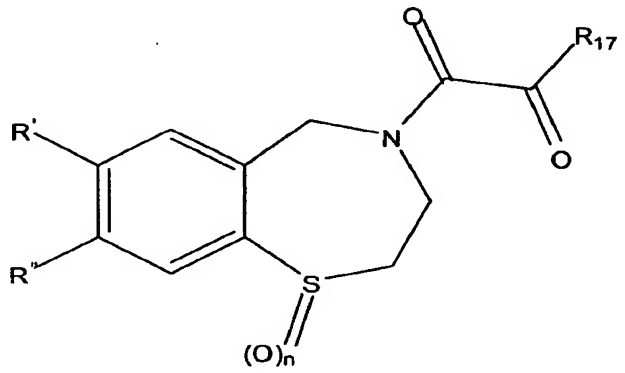
each R, q, and n is as defined in compounds of formula **I-a** above; and enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and pro-drugs thereof.

[00155] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-i**, wherein each R is independently

selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$, Ph, $-NHCH_2Ph$, -C(=O)Me, -OC(=O)Me, morpholinyl and propenyl; and n is 0, 1, or 2.

[00156] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-i**, wherein R_{17} is $-NR_{15}R_{16}$, and $-OR_{15}$. In certain other embodiments, R_{17} is -OH, -OMe, -NEt, -NHEt, -NHPh, $-NH_2$, or -$NHCH_2$pyridyl.

[00157] In one embodiment, the present invention provides methods and uses which comprise administering compounds of formula of **I-j**:



(I-j)

wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-SO_3H$, $-S(=O)_2$alkyl, -S(=O)alkyl, $-OS(=O)_2CF_3$, acyl, alkyl, alkoxyl, alkylamino, alkylthio, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino; and wherein each acyl, alkyl, alkoxyl, alkylamino, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio may be substituted or unsubstituted;

R_{17} is selected from the group consisting of $-NR_{15}R_{16}$, $-NHNR_{15}R_{16}$, -NHOH, $-OR_{15}$, $-CH_2X$, alkenyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each alkenyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted;

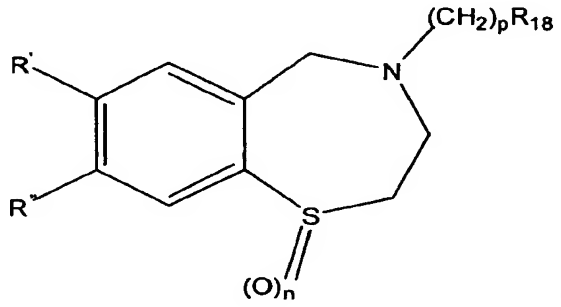
n is as defined in compounds of formula **I-a**; and

enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and pro-drugs thereof.

[00158] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-j**, wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$, Ph, $-NHCH_2Ph$, -C(=O)Me, -OC(=O)Me, morpholinyl and propenyl; and n is 0, 1 or 3. In some cases, R' is H or OMe, and R" is H.

[00159] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-j**, wherein R_{17} is $-NR_{15}R_{16}$ or $-OR_{15}$. In certain other embodiments, R_{17} is -OH, -OMe, -NEt, -NHEt, -NHPh, $-NH_2$, or -$NHCH_2$pyridyl.

[00160] In another embodiment, the present invention provides methods and uses which comprise administering compounds of formula **I-k**:



(I-k)

wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-SO_3H$, $-S(=O)_2$alkyl, -S(=O)alkyl, $-OS(=O)_2CF_3$, acyl, alkyl, alkoxyl, alkylamino, alkylthio, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino; and wherein each acyl, alkyl, alkoxyl, alkylamino, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio may be substituted or unsubstituted;

R_{18} is selected from the group consisting of $-NR_{15}R_{16}$, $-C(=O)NR_{15}R_{16}$, $-(C=O)OR_{15}$, $-OR_{15}$, alkyl, aryl, cycloalkyl, heterocyclyl, and at one labeling group; wherein each alkyl, aryl, cycloalkyl, and heterocyclyl may be substituted or unsubstituted;

wherein p is 1, 2, 3, 4, 5, 6, 7, 8 9, or 10;

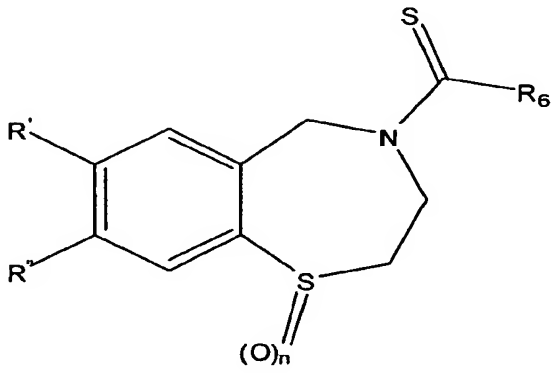
and n is 0, 1, or 2;

and enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and pro-drugs thereof.

[00161] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-k**, wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$, Ph, $-NHCH_2Ph$, -C(=O)Me, -OC(=O)Me, morpholinyl and propenyl; and n is 0, 1 or 3. In some cases, R' is H or OMe, and R" is H.

[00162] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-k**, wherein R_{18} is selected from the group consisting of $-NR_{15}R_{16}$, $-(C=O)OR_{15}$, $-OR_{15}$, alkyl, aryl, and at one labeling group; and wherein each alkyl and aryl may be substituted or unsubstituted. In some cases, m is 1, and R_{18} is Ph, C(=O)OMe, C(=O)OH, aminoalkyl, NH_2, NHOH, or NHCbz. In other cases, m is 0, and R_{18} is C_1-C_4 alkyl, such as Me, Et, propyl, and butyl. In yet other cases, m is 2, and R_{18} is pyrrolidine, piperidine, piperazine, or morpholine. In some embodiments, m is 3, 4, 5, 5, 7, or 8, and R_{18} is a fluorescent labeling group selected from bodipy, dansyl, fluorescein, rhodamine, Texas red, cyanine dyes, pyrene, coumarins, Cascade Blue™, Pacific Blue, Marina Blue, Oregon Green, 4',6-Diamidino-2-phenylindole (DAPI), indopyra dyes, lucifer yellow, propidium iodide, porphyrins, arginine, and variants and derivatives thereof.

[00163] In yet another embodiment, the present invention provides methods and uses which comprise administering compounds of formula of **I-l**:



(I-l)

wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-SO_3H$, $-S(=O)_2$alkyl, -S(=O)alkyl, $-OS(=O)_2CF_3$, acyl,

alkyl, alkoxyl, alkylamino, alkylthio, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino; and wherein each acyl, alkyl, alkoxyl, alkylamino, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio may be substituted or unsubstituted;

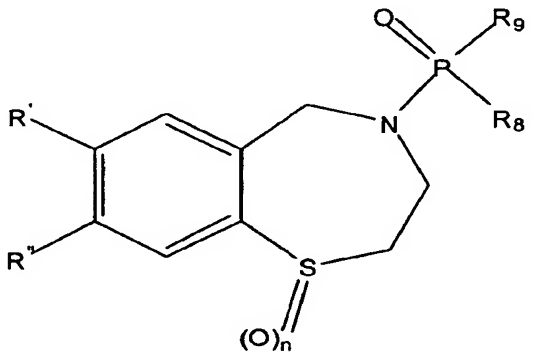
R_6 and n are as defined in compounds of formula **I-a**;

and enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and pro-drugs thereof.

[00164] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-l**, wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$, Ph, $-NHCH_2Ph$, -C(=O)Me, -OC(=O)Me, morpholinyl and propenyl; and n is 0, 1 or 3. In some cases, R' is H or OMe, and R" is H.

[00165] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-l**, wherein R_6 is selected from the group consisting of $-NR_{15}R_{16}$, $-NHNR_{15}R_{16}$, $-OR_{15}$, -NHOH, $-CH_2X$, acyl, alkenyl, alkyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl; wherein each acyl, alkenyl, alkyl, aryl, cycloalkyl, cycloalkylalkyl, heterocyclyl, and heterocyclylalkyl may be substituted or unsubstituted. In some cases, R_6 is $-NR_{15}R_{16}$ such as –NHPh, pyrrolidine, piperidine, piperazine, morpholine, and the like. In some other cases, R_6 is alkoxyl, such as –O-tBu.

[00166] In a further embodiment, the present invention provides methods and uses which comprise administering compounds of formula **I-m**:



(I-m)

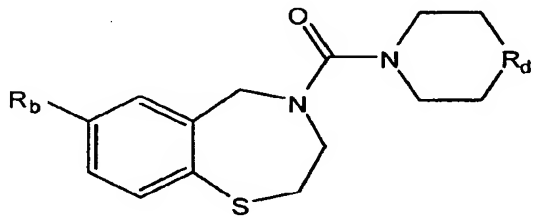
wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-SO_3H$, $-S(=O)_2$alkyl, -S(=O)alkyl, $-OS(=O)_2CF_3$, acyl, alkyl, alkoxyl, alkylamino, alkylthio, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio, and (hetero-)arylamino; and wherein each acyl, alkyl, alkoxyl, alkylamino, cycloalkyl, aryl, heterocyclyl, heterocyclylalkyl, alkenyl, alkynyl, (hetero-)aryl, (hetero-)arylthio may be substituted or unsubstituted;

R_8, R_9 and n are as defined in compounds of formula **I-a** above; and enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, and pro-drugs thereof.

[00167] In certain embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-m**, wherein R' and R" are independently selected from the group consisting of H, halogen, -OH, OMe, $-NH_2$, $-NO_2$, -CN, $-CF_3$, $-OCF_3$, $-N_3$, $-S(=O)_2C_1$-C_4alkyl, $-S(=O)C_1$-C_4alkyl, $-S$-C_1-C_4alkyl, $-OS(=O)_2CF_3$, Ph, $-NHCH_2Ph$, -C(=O)Me, -OC(=O)Me, morpholinyl and propenyl; and n is 0, 1 or 3. In some cases, R' is H or OMe, and R" is H.

[00168] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-m**, wherein R_8 and R_9 are independently alkyl, aryl, -OH, alkoxyl, or alkylamino. In some cases, R_8 is C_1-C_4 alkyl such as Me, Et, propyl and butyl; and R_9 is aryl such as phenyl.

[00169] In other embodiments, the present invention provides methods and uses which comprise administering compounds of formula **I-n**,



I-n

wherein:

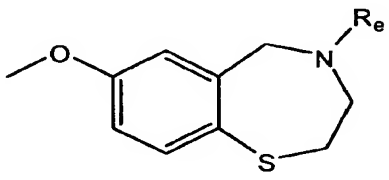
R_d is CH_2, or NR_a; and

R_a is H, –(C_1-C_6 alkyl)-aryl, wherein the aryl is a disubstituted phenyl or a benzo[1,3]dioxo-5-yl group, or an amine protecting group (e.g., a Boc group); and

R_b is hydrogen of alkoxy (e.g., methoxy).

[00170] Representative compounds of Formula **I-n** include without limitation S101, S102, S103, S114.

[00171] In certain other embodiments, the invention provides compounds of Formula **I-o**:



I-o

wherein:

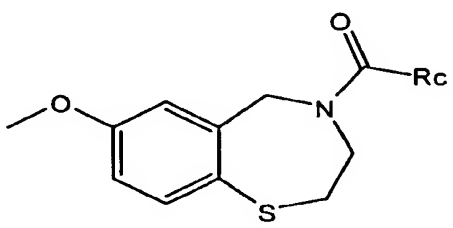
R_e is -(C_1-C_6 alkyl)-phenyl, -(C_1-C_6 alkyl)-C(O)R_b, or substituted or unsubstituted -C_1-C_6 alkyl; and

R_b is –OH or –O-(C_1-C_6 alkyl), and

wherein the phenyl or substituted alkyl is substituted with one or more of halogen, hydroxyl, -C_1-C_6 alkyl, -O-(C_1-C_6 alkyl), -NH_2, -NH(C_1-C_6 alkyl), -N(C_1-C_6 alkyl)$_2$, cyano, or dioxolane.

[00172] Representative compounds of Formula **I-o** include without limitation S107, S110, S111, S120, and S121.

[00173] In certain other embodiments, the invention provides compounds of Formula **I-p**:

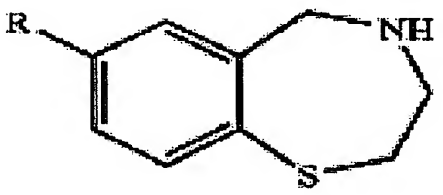


I-p

wherein:

R_c is $-(C_1\text{-}C_6$ alkyl)-NH_2, -(C_1-C_6 alkyl)-OR_f, wherein R_f is H or –C(O)-(C_1-C_6)alkyl, or –(C_1-C_6 alkyl)-NHR_g wherein Rg is carboxybenzyl. Representative compound of Formula **I-p** include without limitation S109, S122, S123.

[00174] In another embodiment, the present invention provides use of compounds of Formula II:



wherein R=OR', SR', NR', alkyl, or halide and R' = alkyl, aryl, or H, and wherein R can be at position 2, 3, 4, or 5. Formula II is discussed also in co-pending application 10/680,988, the disclosure of which is incorporated herein in its entirety by reference.

[00175] In non-limiting examples, Formulae-Ia, Ib, Ie, If, Ig, Ih, In are represented by compounds S101, S102, S103. In a non-limiting example, Formulae Ia, Ib, Ie, If, Ii, Ij are represented by compound S104. In a non-limiting example, Formulae Ia, Ib, Io are represented by S107. In a non-limiting example, Formulae Ia, Ib, Ie, If are represented by S108. In a non-limiting example, Formulae Ia, Ib, Ie, If, Ip are represented by S109. In a non-limiting example, Formulae Ia, Ib, Ik, Io are represented by S110. In a non-limiting example, Formulae Ia, Ib, Ik, Io are represented by S111. In a non-limiting example, Formulae Ia, Ib, Ic, Id are represented by S112. In a non-limiting example, Formulae Ia, Ib are represented by S113. In a non-limiting example, Formulae Ia, Ib, Ie, If, Ig, Ih are represented by S114. In a non-limiting example, Formulae Ia, Ib, Ig, Ih, Il are represented by S115. In a non-limiting example, Formulae Ia, Ib, Ig, Ih, are represented by S116. In a non-limiting example, Formulae Ia, Ib, Ie, If are represented by S117. In a non-limiting example, Formulae Ia, Ib, Ie, If are represented by S118. In a non-limiting example, Ia, Ib are represented by S119. In a non-limiting example, Formulae Ia, Ib, Ik, Io are represented by S120. In a non-limiting example, Formulae Ia, Ib, Ik, Io, Ip are represented by S121. In a non-limiting example,

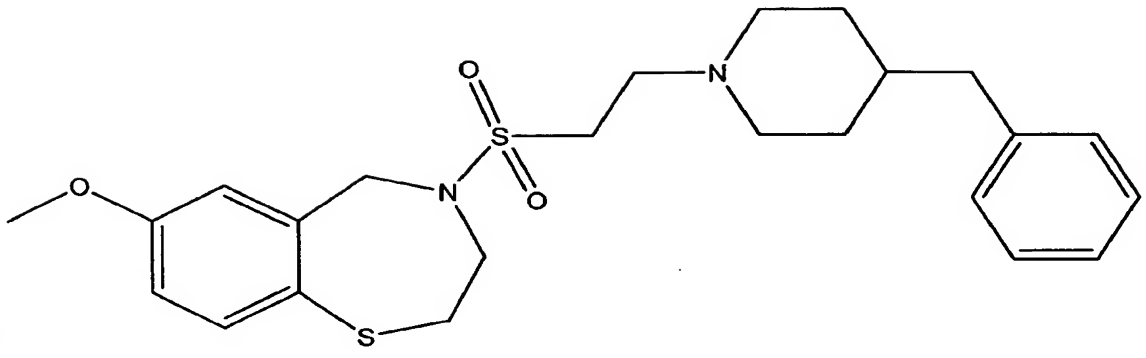
Formulae Ia, Ib, Ie, If, Ip are represented by S122. In a non-limiting example, Formulae Ia, Ib, Ie, If, Ip are represented by S123.

[00176] Other embodiments of the compounds of any of formulae Formula I-a, I-b, I-e, I-f, I-g, I-h, I-i, I-j, I-k, I-n, I-o, or I-p are provided in PCT/US2006/32405, U.S. Application Nos. 11/809,470 11/212,309, 11/506,285, and 11/212,413, the contents of which are hereby incorporated by reference in their entirety.

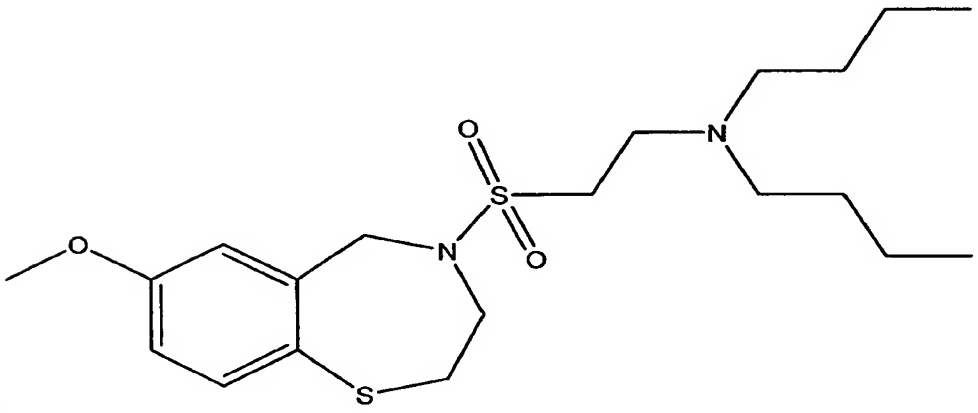
[00177] Examples of compounds that may be used in conjunction with the invention include, without limitation, S1, S2, S3, S4, S5, S6, S7, S9, S11, S12, S13, S14, S19, S20, S22, S23, S24, S25, S26, S27, S36, S37, S38, S40, S43, S44, S45, S46, S47, S48, S49, S50, S51, S52, S53, S54, S55, S56, S57, S58, S59, S60, S61, S62, S63, S64, S66, S67, S68, S69, S70, S71, S72, S73, S74, S75, S76, S77, S78, S79, S80, S81, S82, S83, S84, S85, S86, S87, S88, S89, S90, S91, S92, S93, S94, S95, S96, S97, S98, S99, S100, S101, S102, S103, S104, S105, S107, S108, S109, S110, S111, S112, S113, S114, S115, S116, S117, S118, S119, S120, S121, S122, and S123, the structures of which are provided below. In certain embodiments, the compounds are isolated and substantially pure.

[00178] In a certain embodiment of the methods the compound is not S4. In another embodiment, the compound is not S7. In another embodiment, the compound is not S8. In another embodiment, the compound is not S10. In another embodiment, the compound is not S20. In another embodiment, the compound is not S24. In another embodiment, the compound is not S25. In another embodiment, the compound is not S26. In another embodiment, the compound is not S27. In another embodiment, the compound is not S36. In another embodiment, the compound is not any one of S1-100. In another embodiment, the compound is not JTV-519.

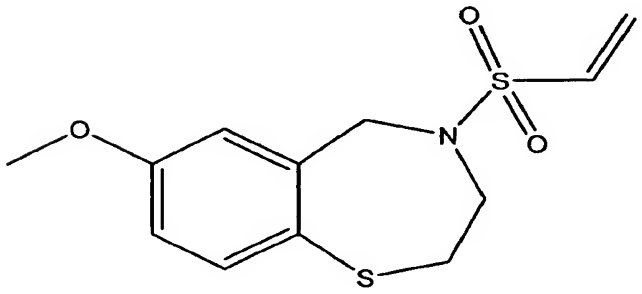
[00179] The named "S" compounds described herein have the following structures:



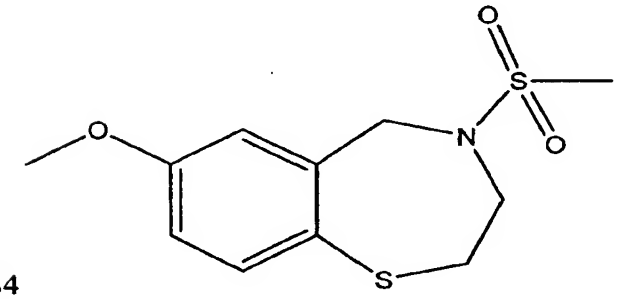
S1



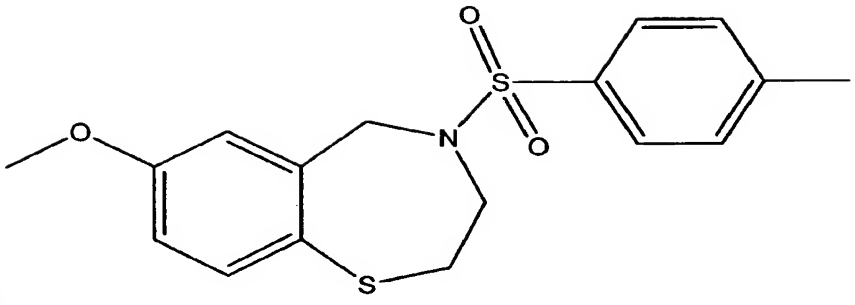
S2



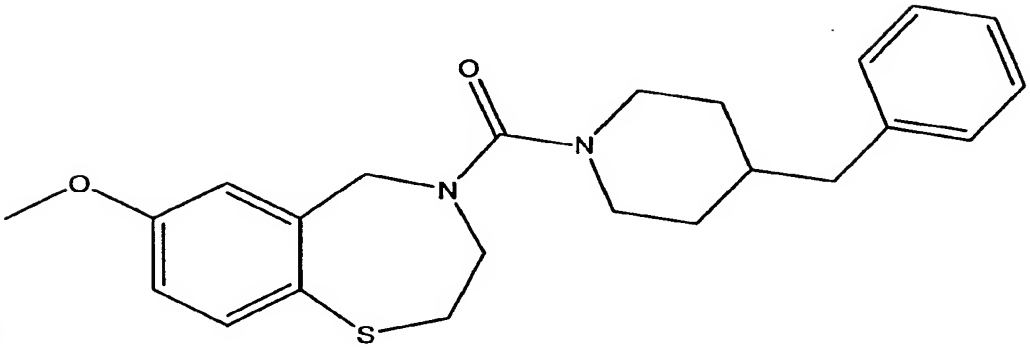
S3



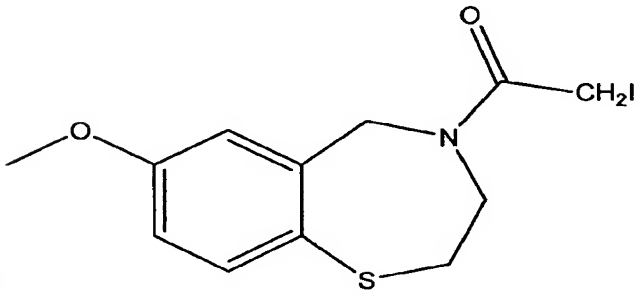
S4



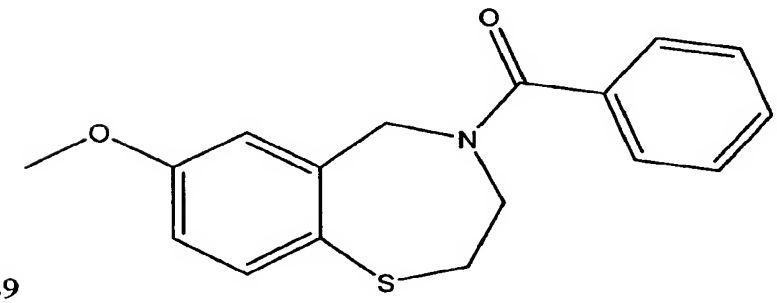
S5



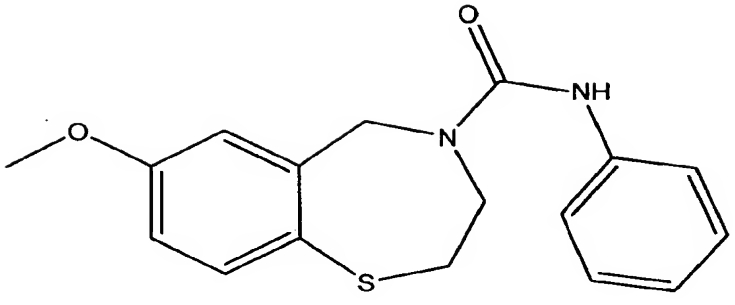
S6



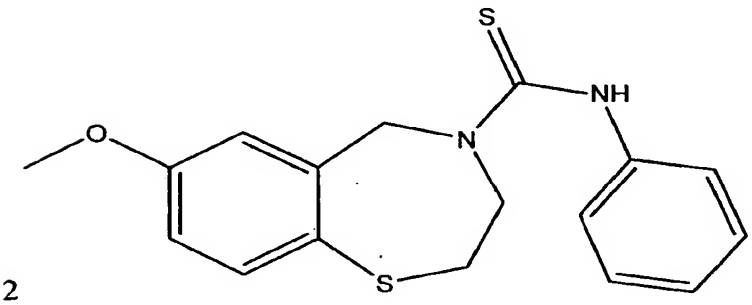
S7



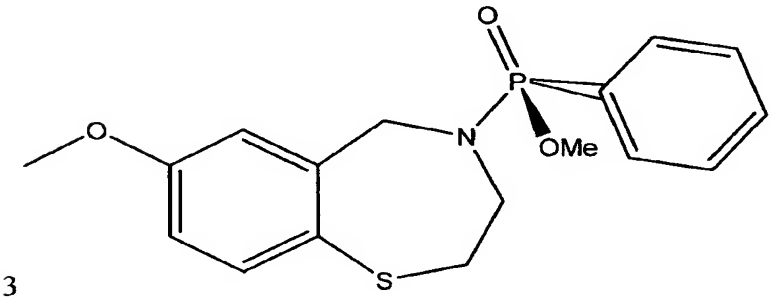
S9



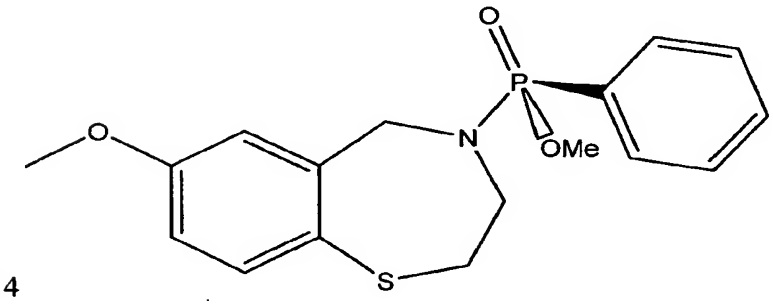
S11



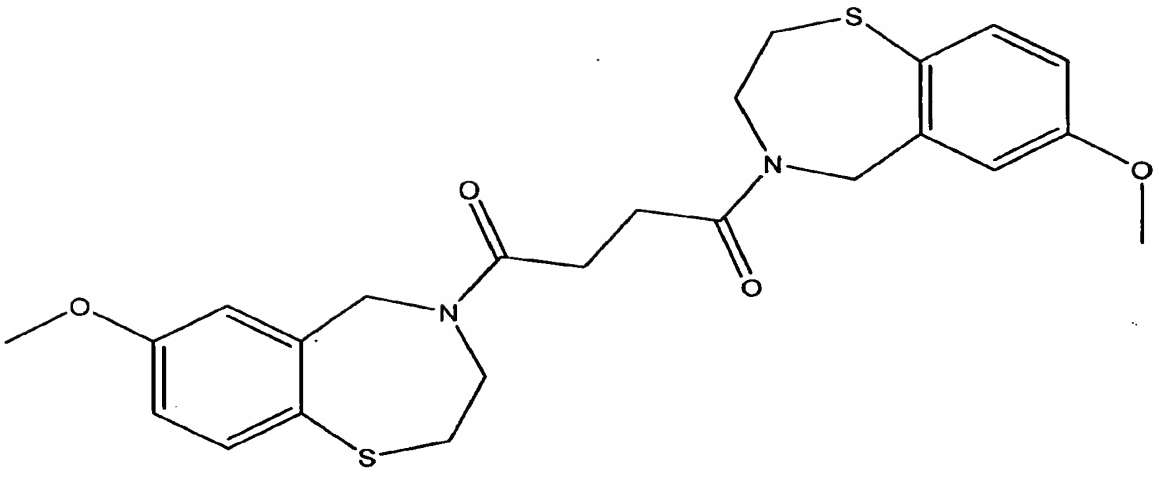
S12



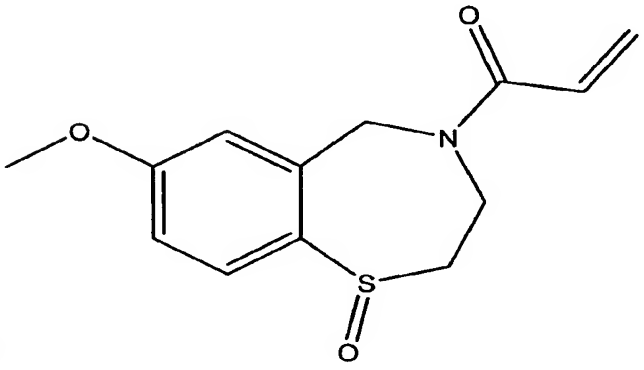
S13



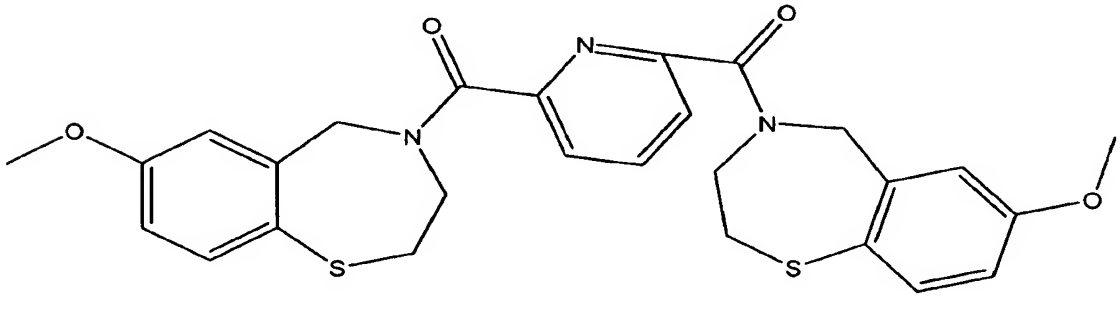
S14



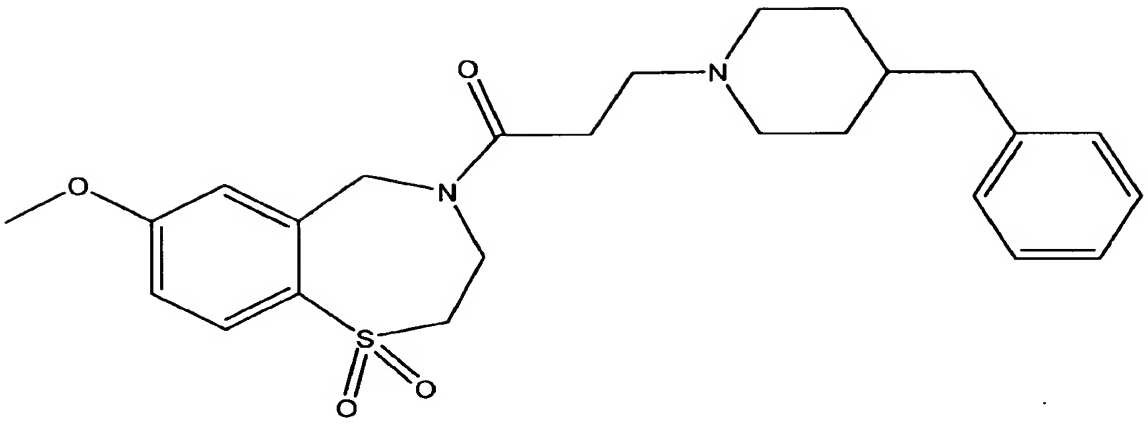
S19



S20

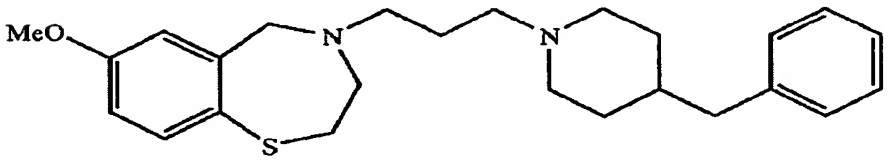


S22

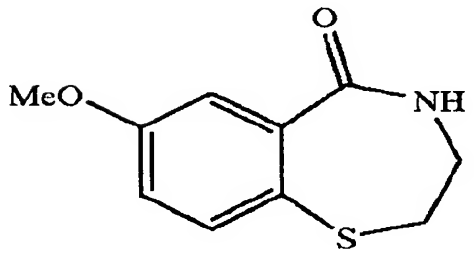


S23

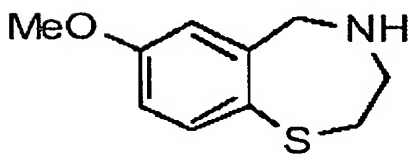
S-24



S24

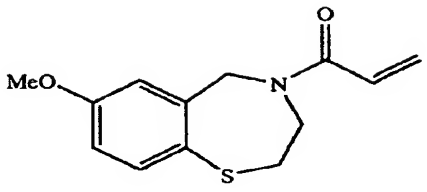


S25

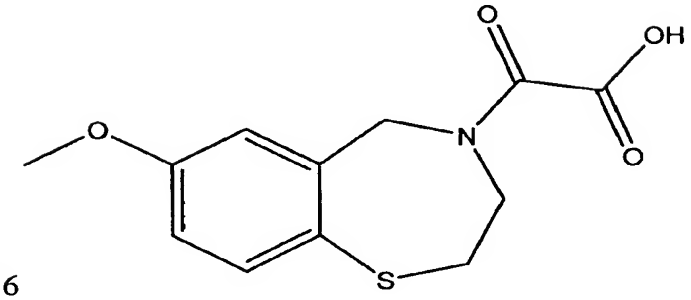


S26

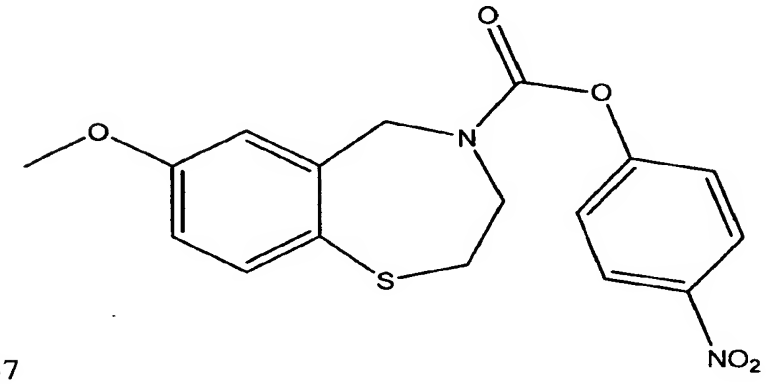
S27



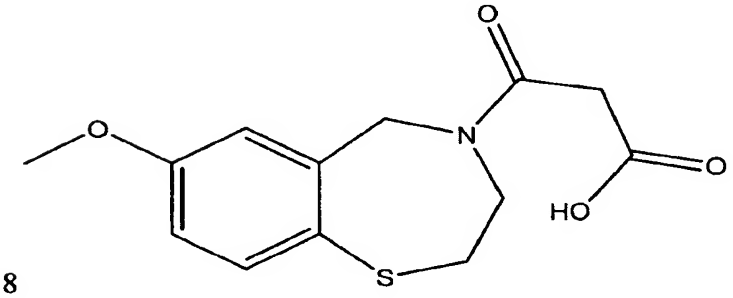
S36

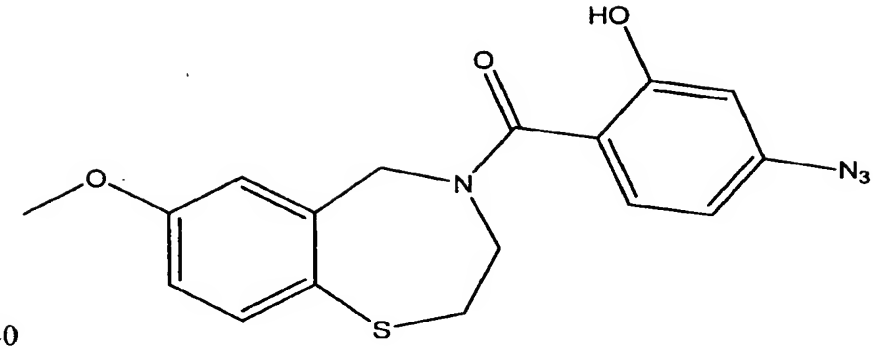


S37

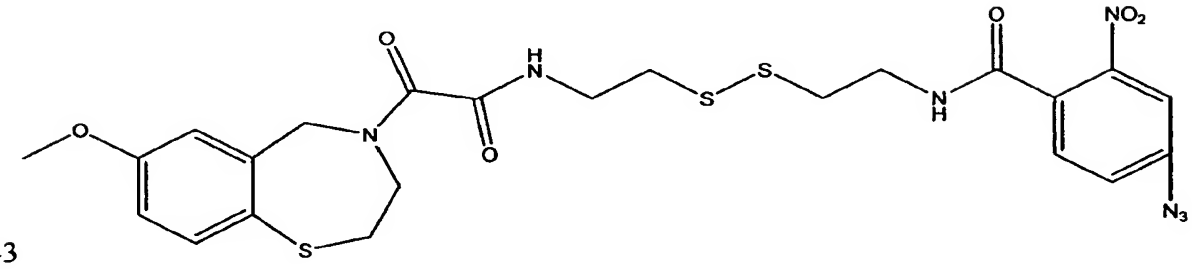


S38

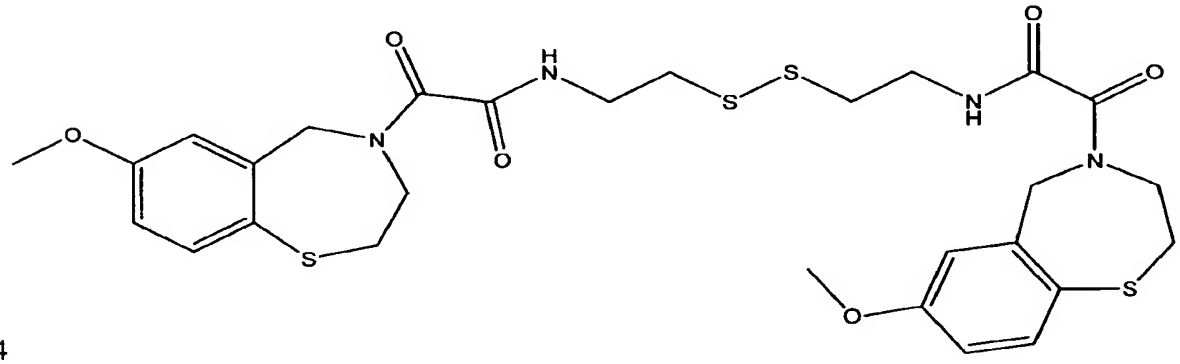




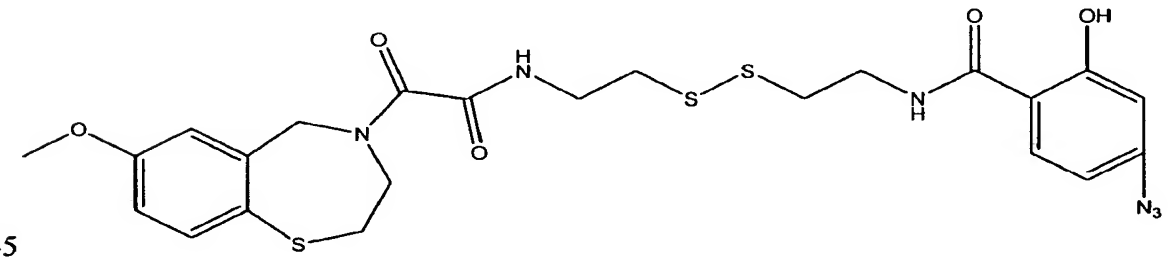
S40



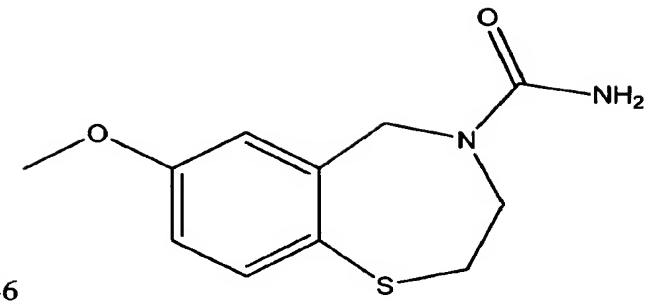
S43



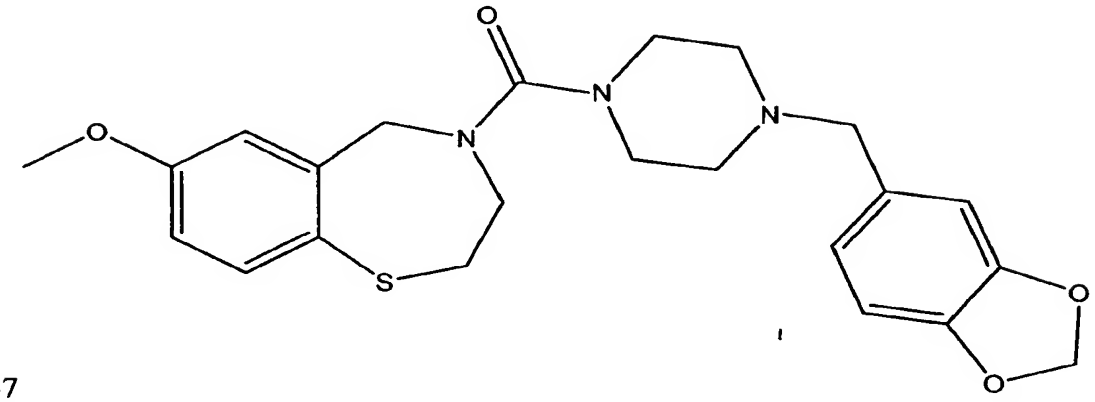
S44



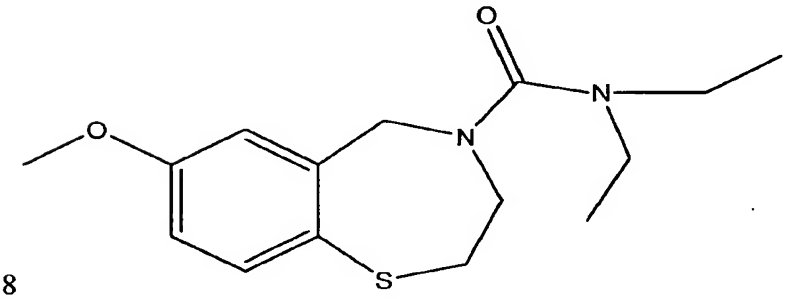
S45



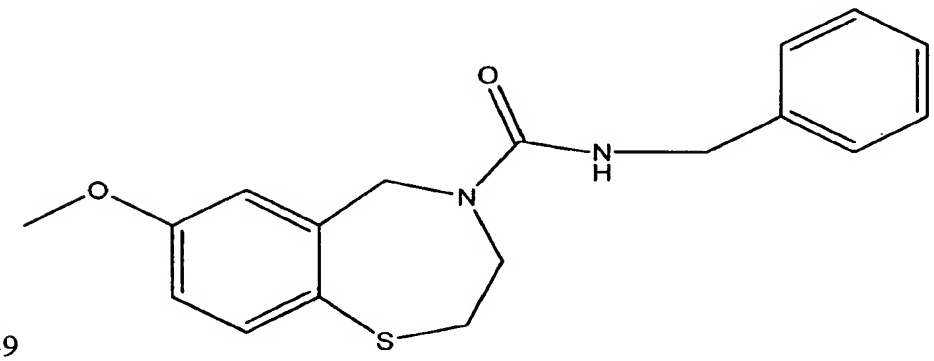
S46



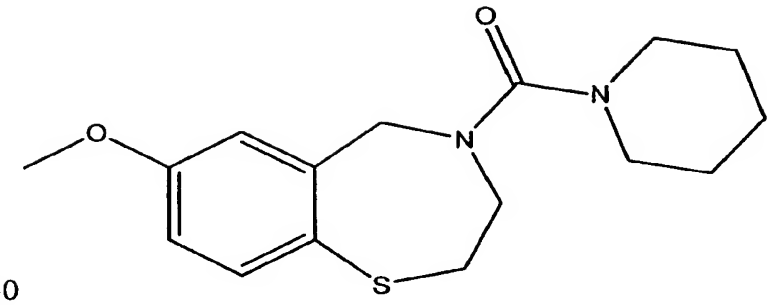
S47



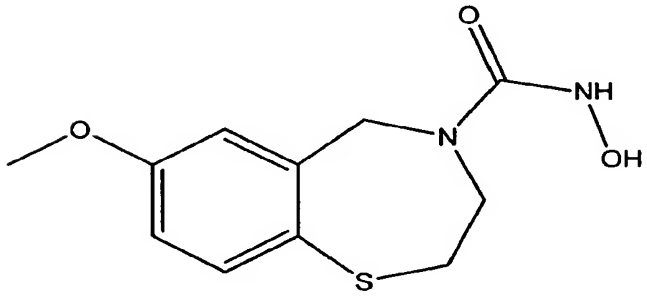
S48



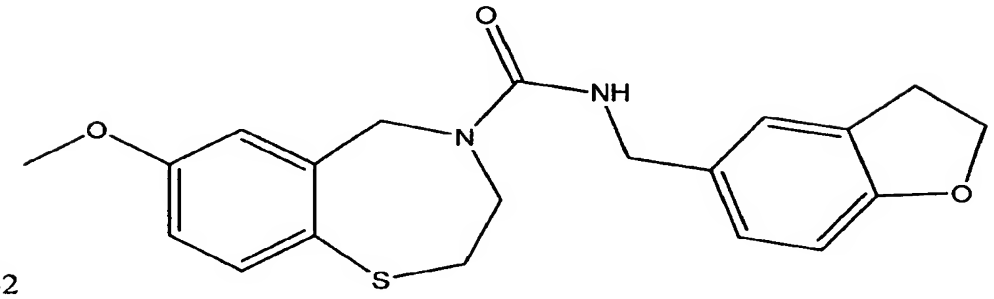
S49



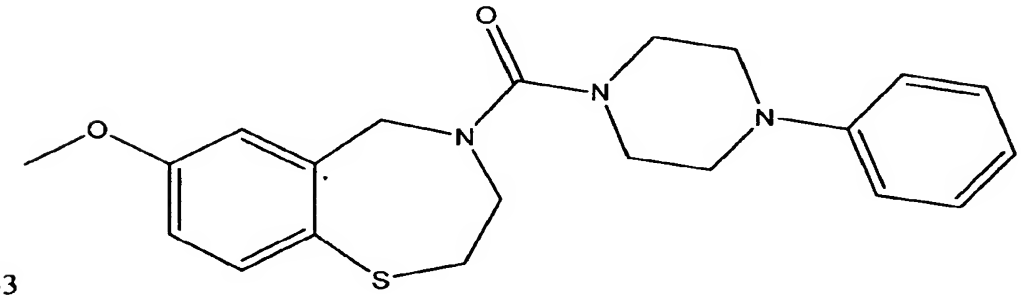
S50



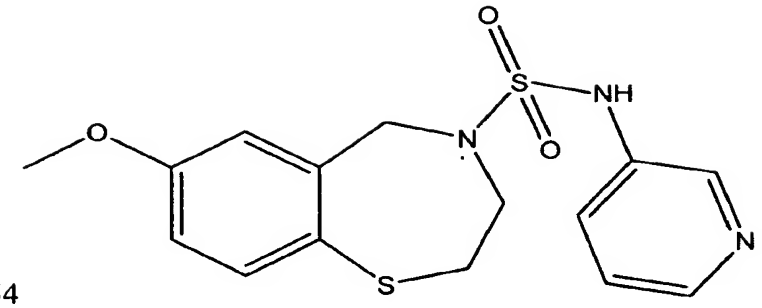
S51



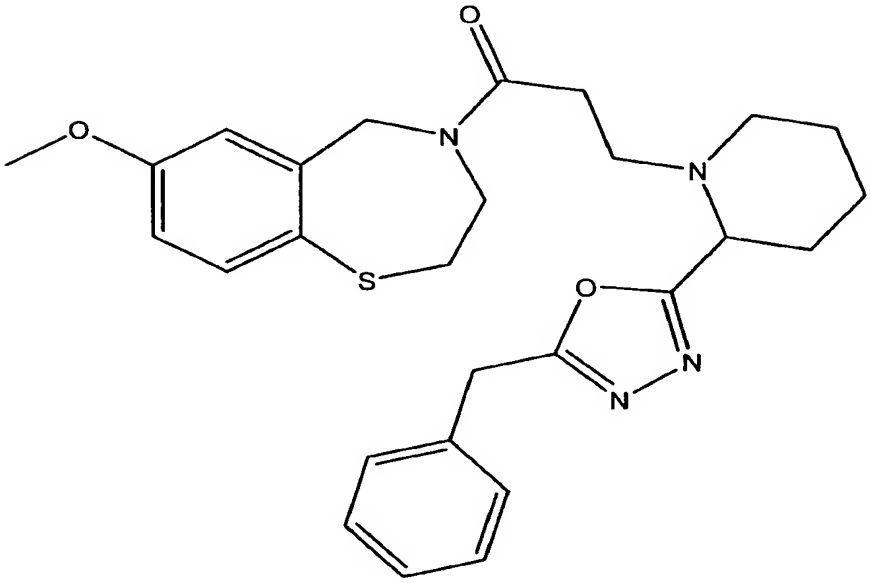
S52



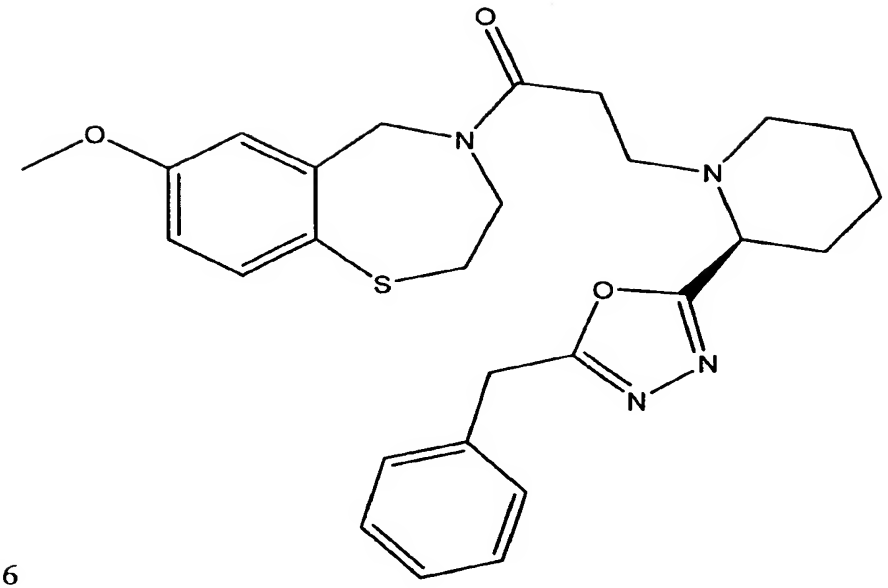
S53



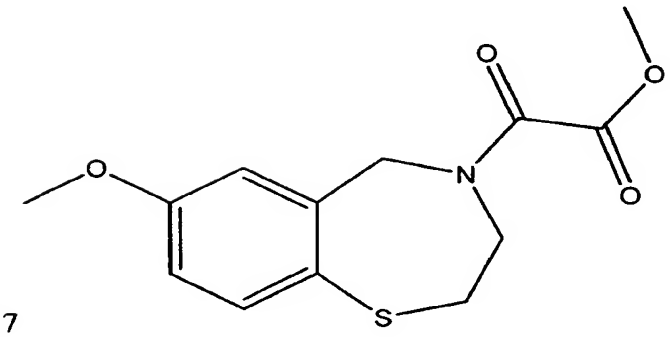
S54



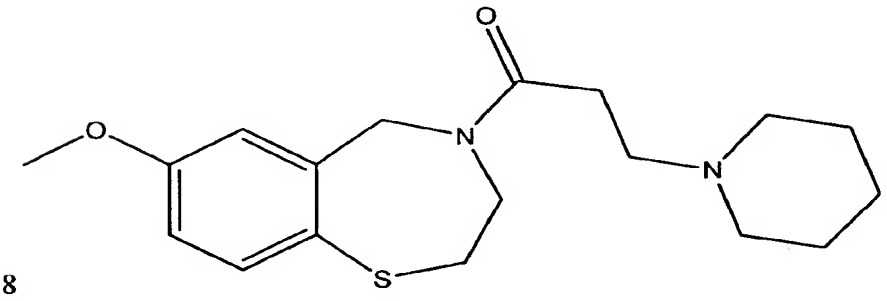
S55



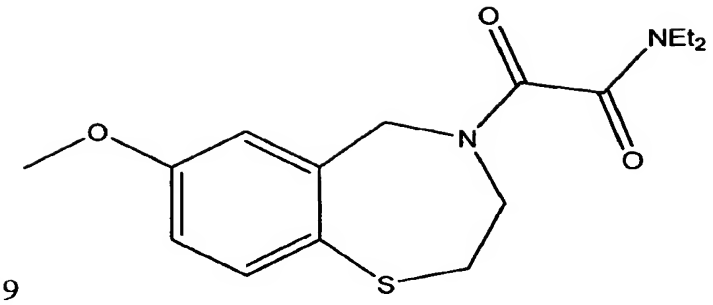
S56



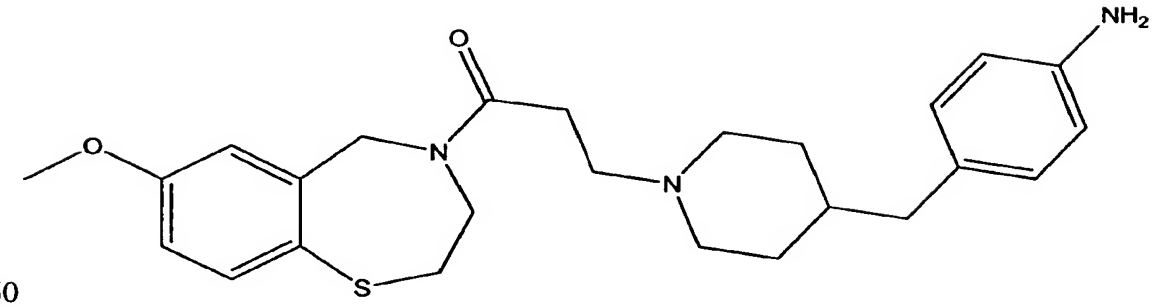
S57



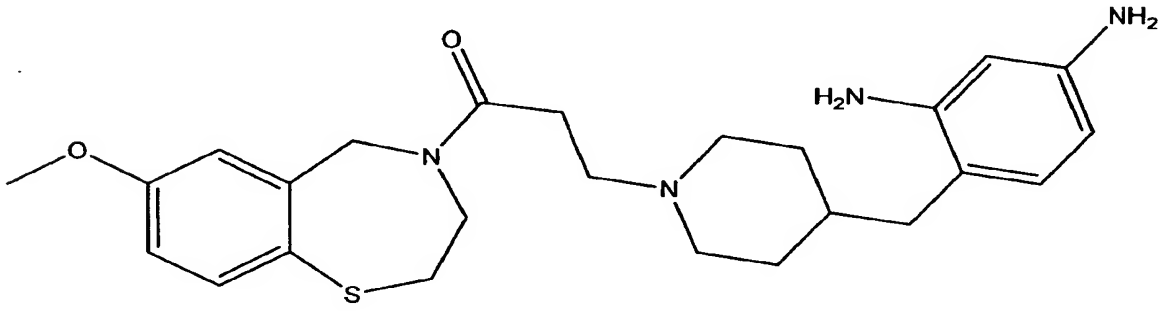
S58



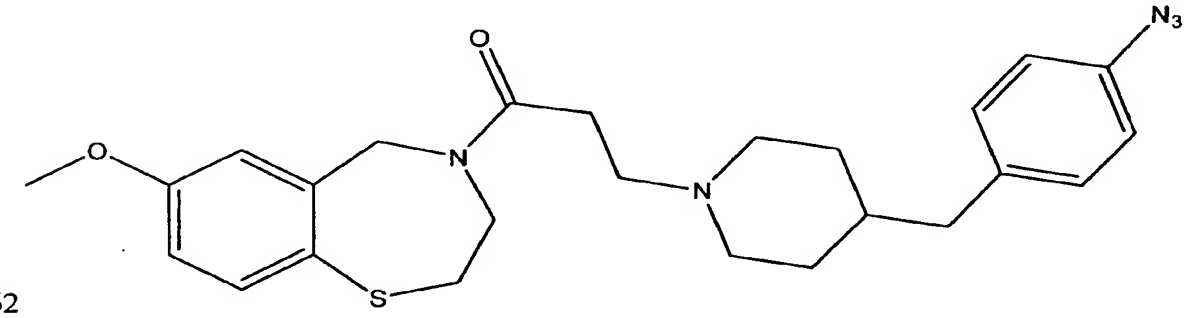
S59



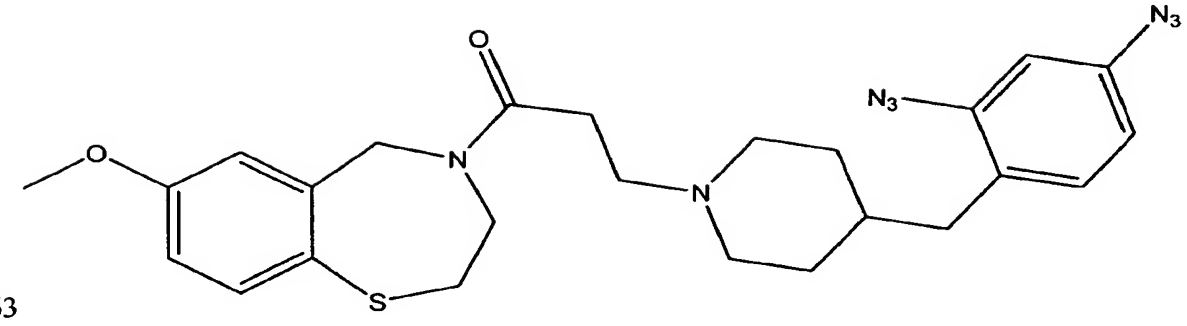
S60



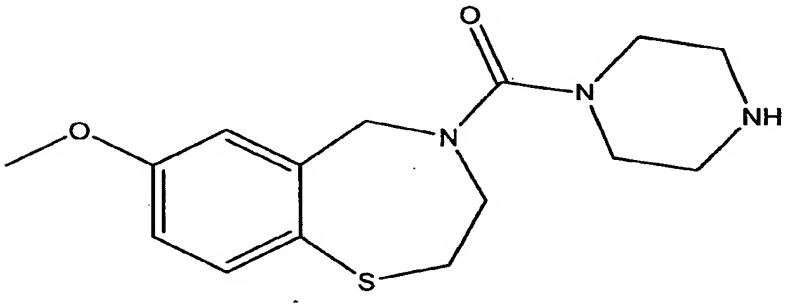
S61



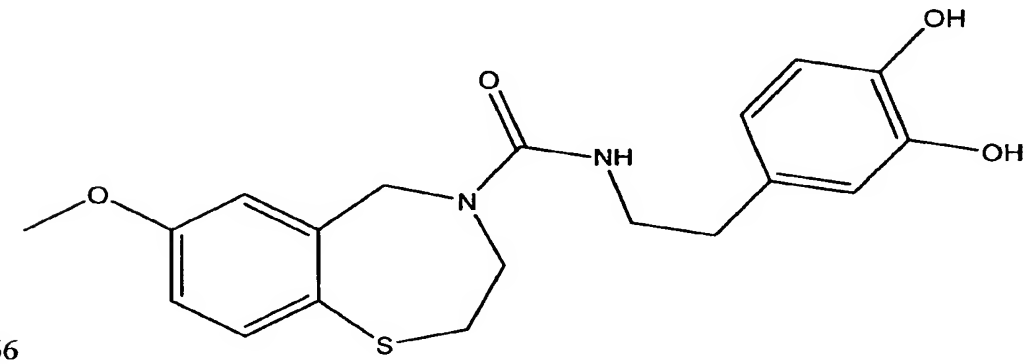
S62



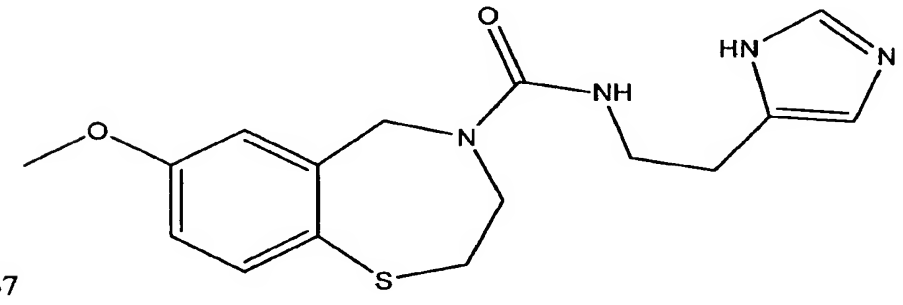
S63



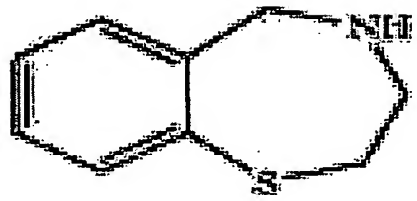
S64



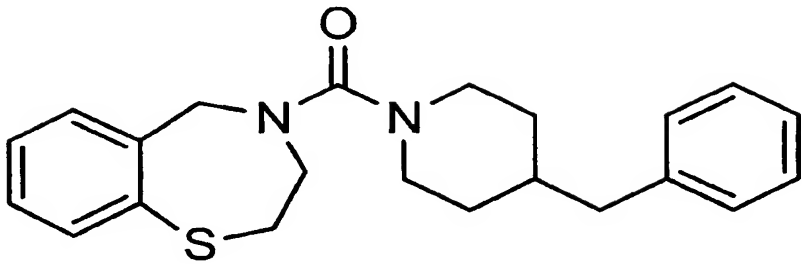
S66



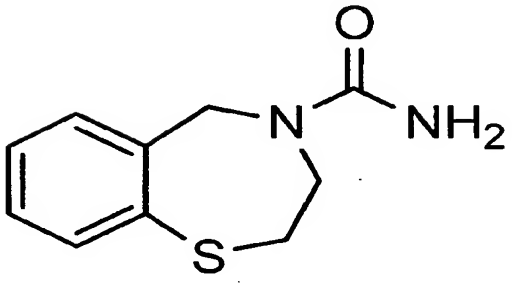
S67



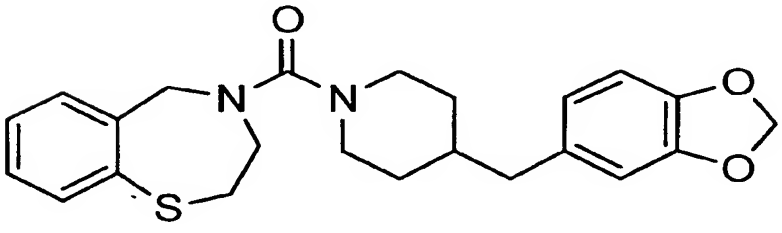
S68



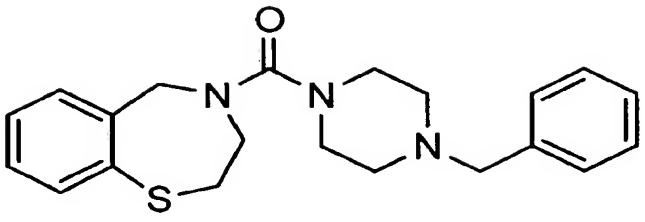
S69



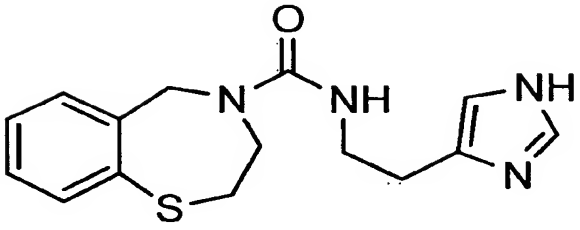
S70



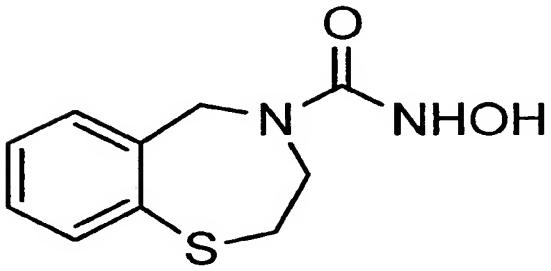
S71



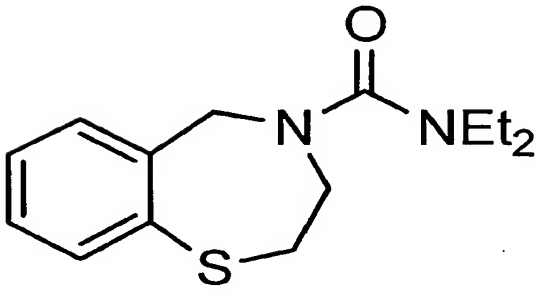
S72



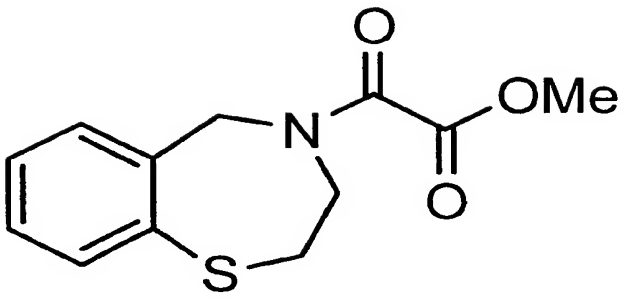
S73



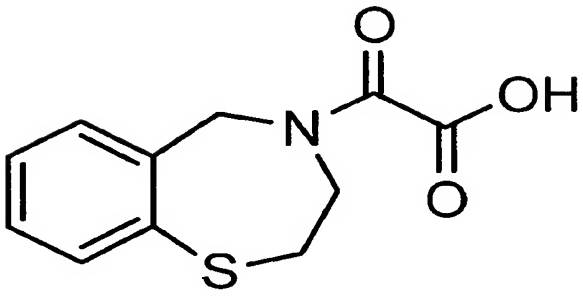
S74



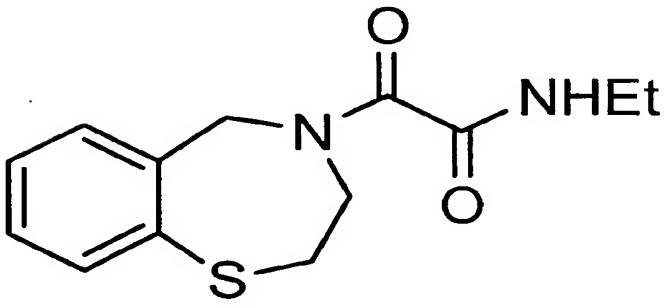
S75



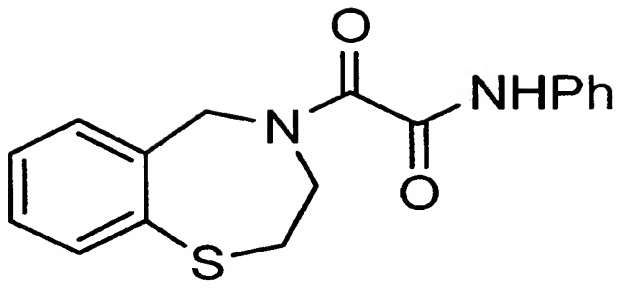
S76



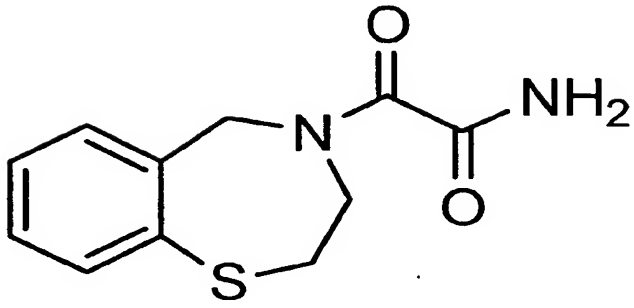
S77



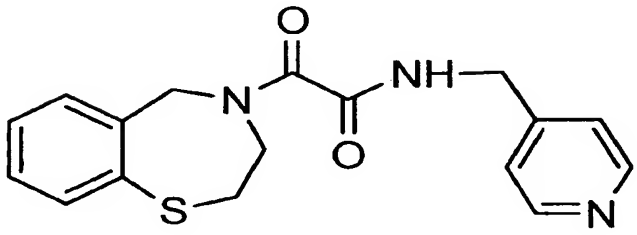
S78



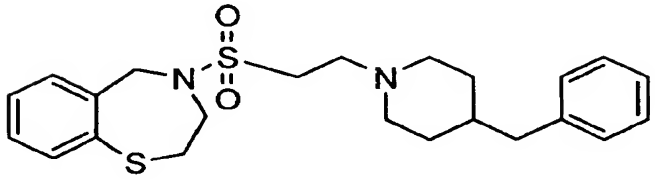
S79



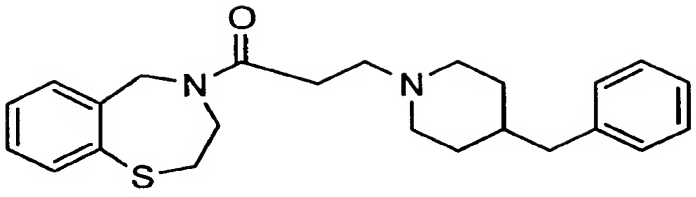
S80



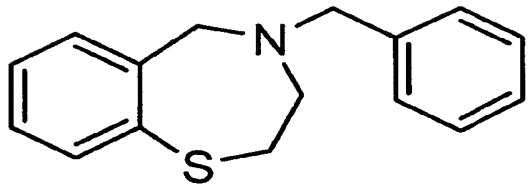
S81



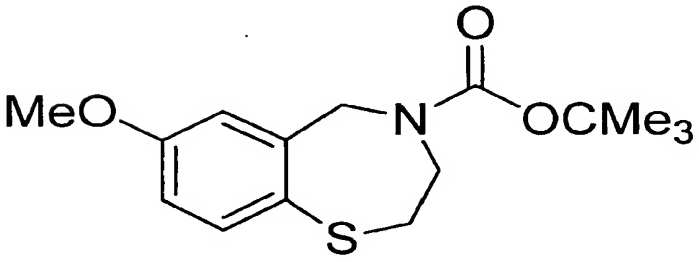
S82



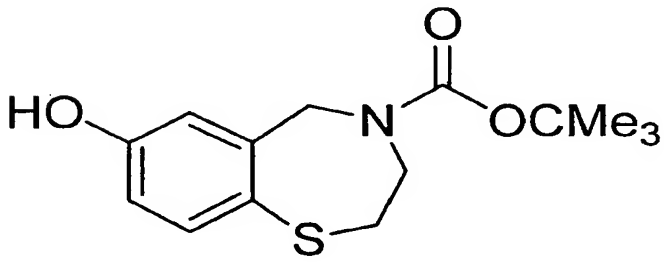
S83



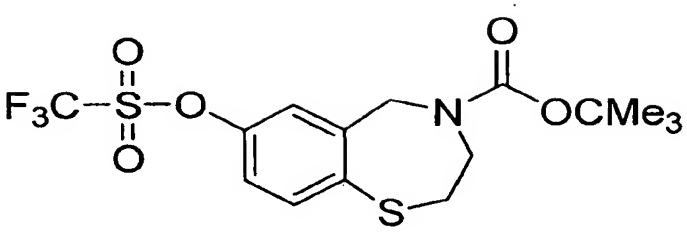
S84



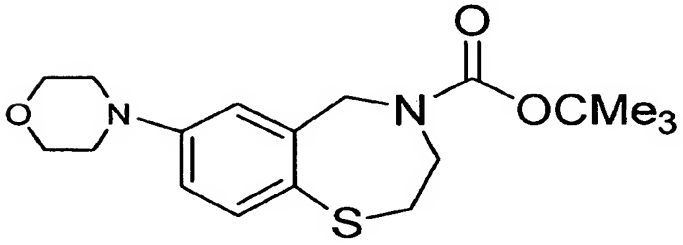
S85



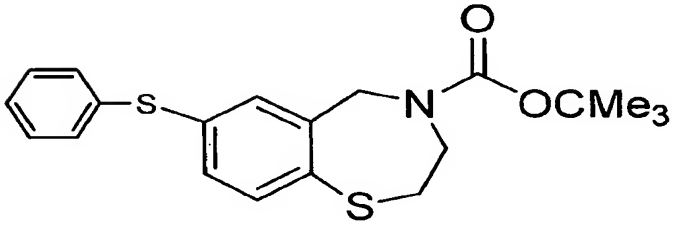
S86



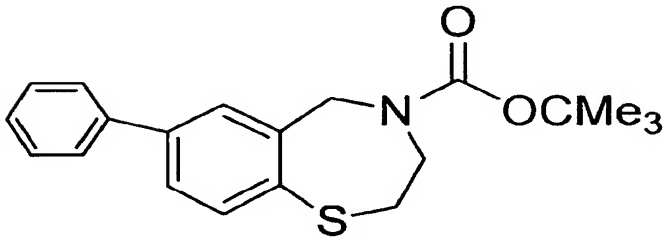
S87



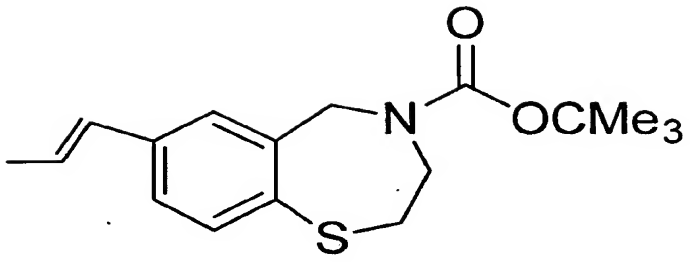
S88



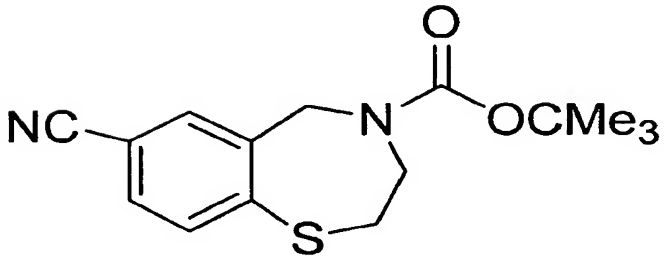
S89



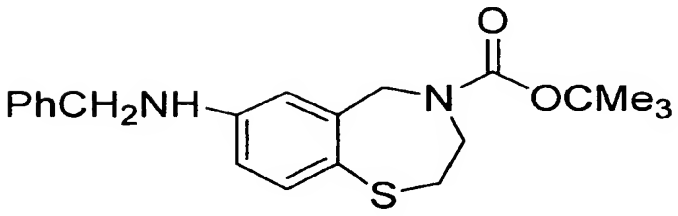
S90



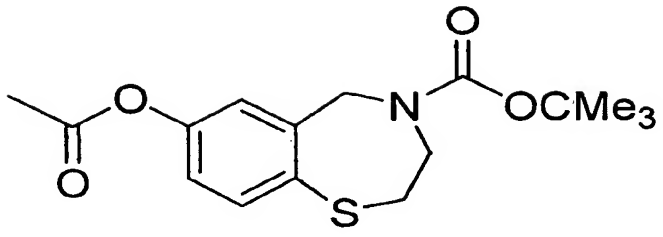
S91



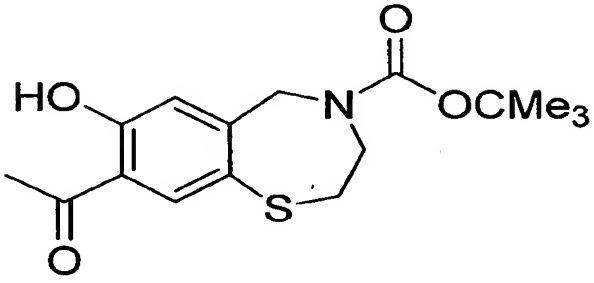
S92



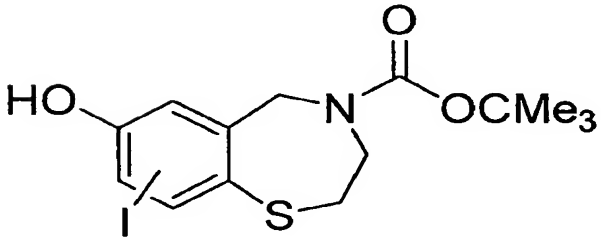
S93



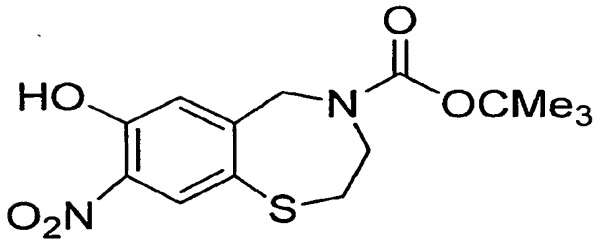
S94



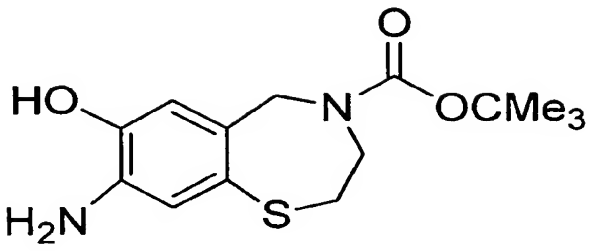
S95



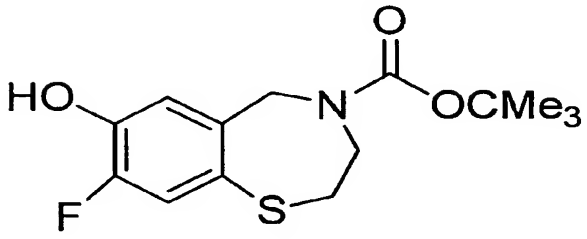
S96



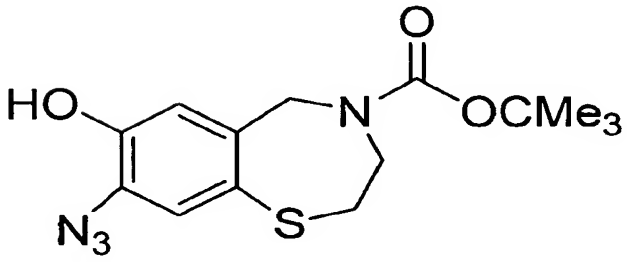
S97



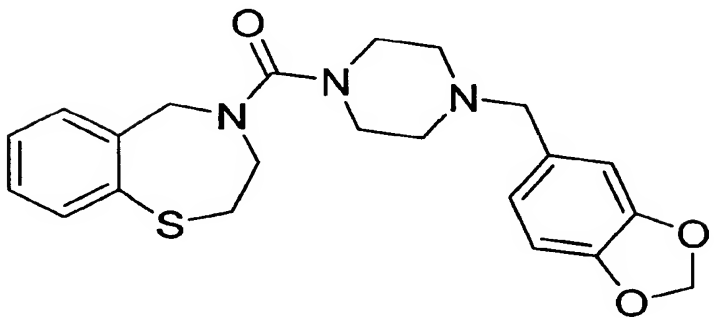
S98



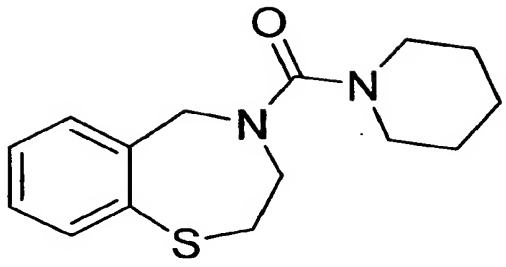
S99



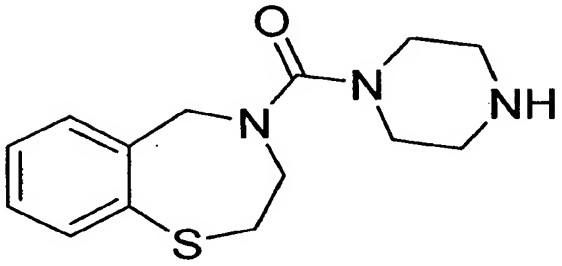
S100



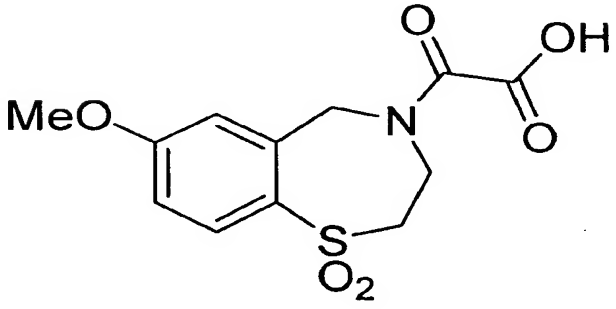
S101



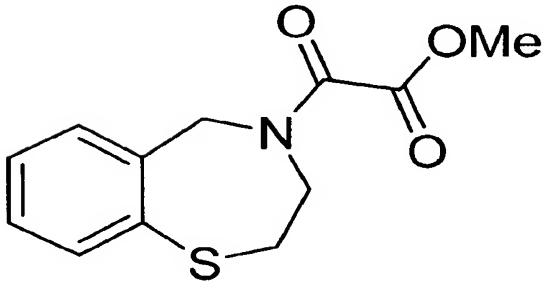
S102



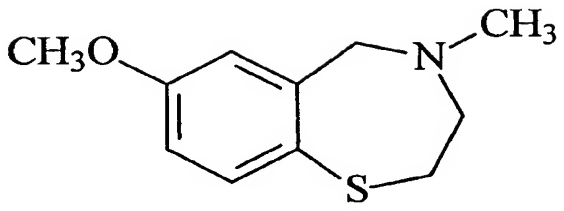
S103



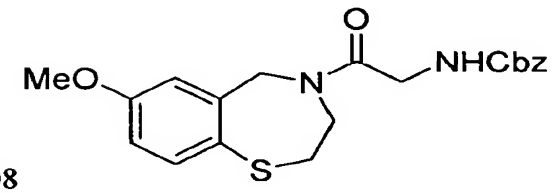
S104



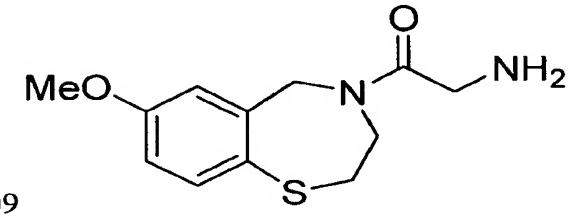
S105



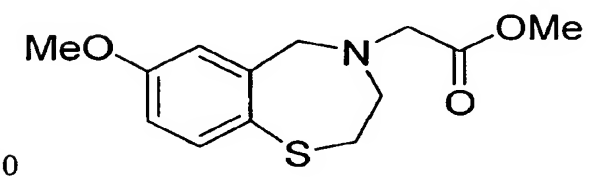
S107



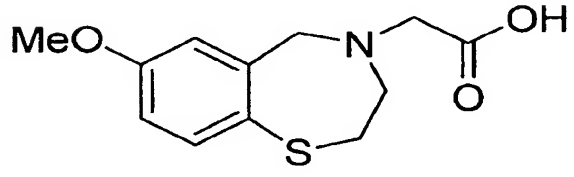
S108



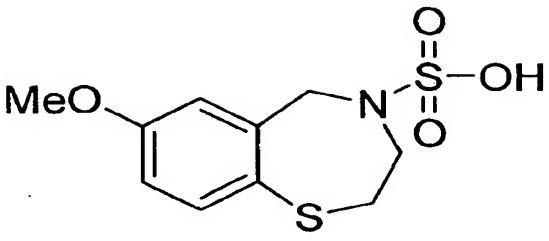
S109



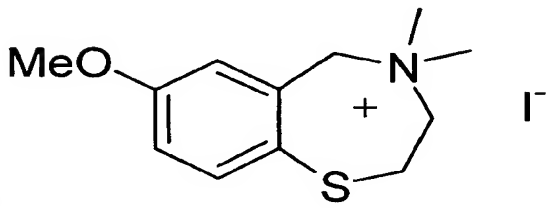
S110



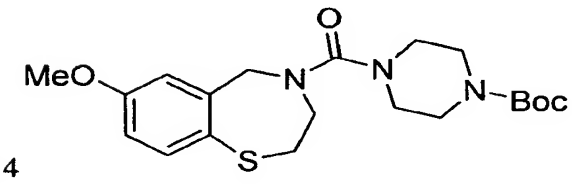
S111



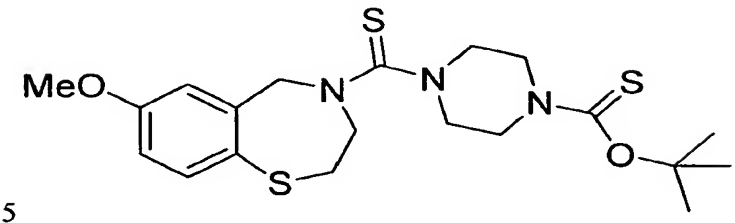
S112



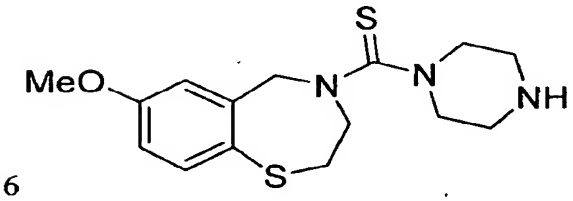
S113



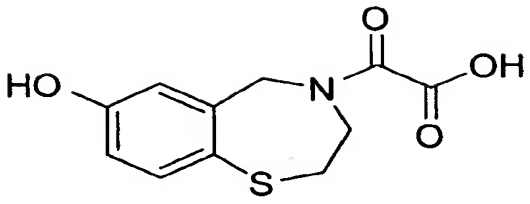
S114



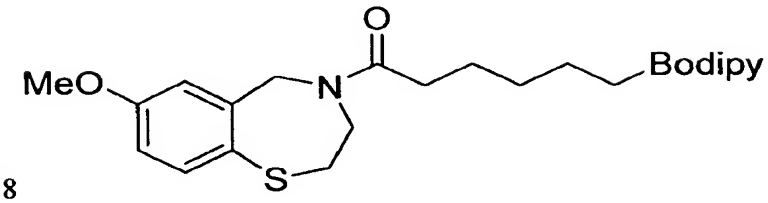
S115



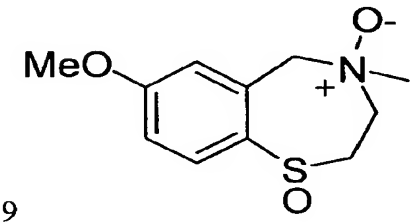
S116



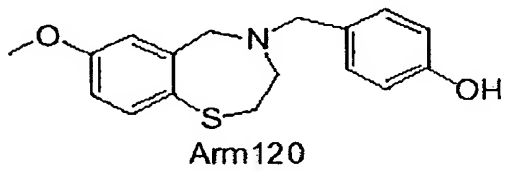
S117



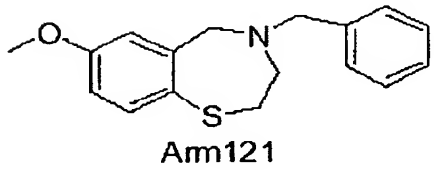
S118



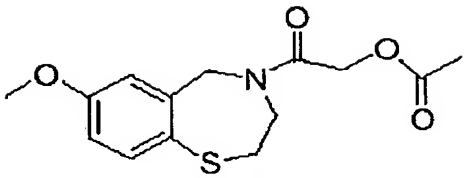
S119



S120

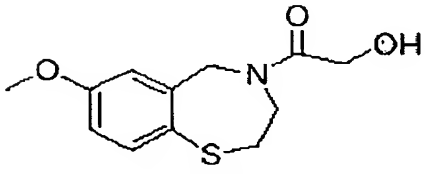


S121



Arm122

S122



Arm123

S123

Routes of Activity

[00180] The compounds of the invention, such as the compounds of Formula I, I-a, I-b, I-c, I-d, I-e, I-f, I-g, I-h, I-i, I-j, I-k, I-l, I-m, I-n, I-o, I-p, and Formula II, reduce the open probability of RyR channels and decrease the calcium current through such or calstabin, and FKBP12.6 or calstabin2) binding affinity. Therefore, the compounds of the invention are useful for the treatment and/or prevention of disorders and conditions associated with abnormal function of RyR receptors, particularly RyR1, RyR2 and RyR3 receptors, where such disorders and conditions are characterized by an increase in the open probability of, and in increase in the calcium current through, RyR receptor channels.

[00181] In accordance with the methods of the present invention, a "decrease" or "disorder" in the level of RyR-bound FKBP in cells of a subject refers to a detectable decrease, diminution or reduction in the level of RyR-bound FKBP in cells of the subject. Such a decrease is limited or prevented in cells of a subject when the decrease is in any way halted, hindered, impeded, obstructed or reduced by the administration of compounds of the invention, such that the level of RyR-bound FKBP in cells of the subject is higher than it would otherwise be in the absence of the administered compound.

[00182] The level of RyR-bound FKBP in a subject is detected by standard assays and techniques, including those readily determined from the known art (*e.g.*, immunological

techniques, hybridization analysis, immunoprecipitation, Western-blot analysis, fluorescence imaging techniques and/or radiation detection, etc.), as well as any assays and detection methods disclosed herein. For example, protein is isolated and purified from cells of a subject using standard methods known in the art, including, without limitation, extraction from the cells (*e.g.*, with a detergent that solubilizes the protein) where necessary, followed by affinity purification on a column, chromatography (*e.g.*, FTLC and HPLC), immunoprecipitation (with an antibody), and precipitation (*e.g.*, with isopropanol and a reagent such as Trizol). Isolation and purification of the protein is followed by electrophoresis (*e.g.*, on an SDS-polyacrylamide gel). A decrease in the level of RyR-bound FKBP in a subject, or the limiting or prevention thereof, is determined by comparing the amount of RyR-bound FKBP detected prior to the administration of JTV-519 or any of the compounds described herein (in accordance with methods described below) with the amount detected a suitable time after administration of the compound.

[00183] A decrease in the level of RyR-bound FKBP in cells of a subject is limited or prevented, for example, by inhibiting dissociation of FKBP and RyR in cells of the subject; by increasing binding between FKBP and RyR in cells of the subject; or by stabilizing the RyR-FKBP complex in cells of a subject. As used herein, the term "inhibiting dissociation" includes blocking, decreasing, inhibiting, limiting or preventing the physical dissociation or separation of an FKBP subunit from an RyR molecule in cells of the subject, and blocking, decreasing, inhibiting, limiting or preventing the physical dissociation or separation of an RyR molecule from an FKBP subunit in cells of the subject. As further used herein, the term "increasing binding" includes enhancing, increasing, or improving the ability of phosphorylated RyR to associate physically with FKBP (*e.g.*, binding of approximately two fold or, approximately five fold, above the background binding of a negative control) in cells of the subject and enhancing, increasing or improving the ability of FKBP to associate physically with phosphorylated RyR (*e.g.*, binding of approximately two fold, or, approximately five fold, above the background binding of a negative control) in cells of the subject. Additionally, a decrease in the level of RyR-bound FKBP in cells of a subject is limited or prevented by directly decreasing the level of phosphorylated RyR in cells of the subject or by indirectly decreasing the level of phosphorylated RyR in the cells (*e.g.*, by targeting an enzyme (such as PKA) or another endogenous molecule that regulates or modulates the functions or levels of phosphorylated RyR in the cells). In one embodiment, the level of phosphorylated RyR in the cells is decreased by at least 10% in the method of the

present invention. In another embodiment, the level of phosphorylated RyR is decreased by at least 20%..

Methods of Synthesis

[00184] The compounds of the present invention may be synthesized as described in published PCT application WO 07/024717 and U.S. patent application 11/506,285, the contents of which are hereby incorporated by reference.

EXAMPLES

EXAMPLE 1 – EFFICACY OF COMPOUNDS

[00185] The compounds described herein increase binding of FKBP12.6 or calstabin2 to RyR2, as illustrated in Table 1. The EC_{50} shown in Table 1 was obtained using an FKBP12.6 rebinding assay to determine the amount of FKBP12.6 binding to PKA-phosphorylated RyR2 at various concentrations (0.5 – 1000 nM) of the compounds shown in Table 1. The EC_{50} values were calculated using Michaelis-Menten curve fitting. Further details of the efficacy of these compounds, and the methods used to assess their efficacy, can be found in published PCT application WO 07/024717 and U.S. patent application 11/506,285 (US 2007/173482), the contents of which are hereby incorporated by reference.

Table 1

Compound No.	EC50 (nM)	Compound No.	EC50 (nM)
1	150	50	40
2	211	51	175
4	102	52	143
5	208	53	200
6	252	54	77
7	55	55	111
9	205	56	95
11	181	57	73
12	197	58	55
13	174	59	102
14	182	60	68
19	265	61	95
22	355	62	45
23	268	63	52
25	40	64	44
26	40	66	110
27	ca. 50	67	89
36	15	68	ca. 100
38	44	74	220
40	100	75	150
43	80	76	25
44	121	77	60
45	80	101	105
46	150	102	135
47	20	104	111
48	100	107	190
49	81		

EXAMPLE 2 - PREPARATION OF TISSUE LYSATES

[00186] Tissue lysates were prepared by homogenizing the tissue (e.g., brain, cardiac, muscle) with Tissuemiser in 0.7ml lysis buffer (pH 7.4, 10mM HEPES, 1mM EDTA, 20mM NaF, 2mM Na_3VO_4, 320mM sucrose, and protease inhibitors) and centrifuged for 15min at 4,000 x g at 4°C. The supernatant was then centrifuged for 15 min at 10,000 x g at 4°C. For brain homogenates, the supernatant was centrifuged at 50,000 x g at 4°C for 30 minutes, and the pellet (microsomes) was resuspended in homogenization buffer which was supplemented with 0.9% NaCl. For brain tissue, the resuspended pellet was used for immunoprecipitation of RyR. For cardiac and muscle tissue homogenates, the supernatant of the 10,000xg spin was used for immunoprecipitation of the RyR. Protein concentrations were measured by Bradford protein assay. The sample was frozen at -80°C until use.

EXAMPLE 3 - IMMUNOPRECIPITATION OF RYANODINE RECEPTORS (RyRs)

[00187] 100μg of microsomes were brought to a volume of 500μl with modified RIPA buffer (50 mM Tris-HCl (pH 7.4), 0.9% NaCl, 5.0 mM NaF, 1.0 mM Na_3VO_4, 0.5% Triton-X100, and protease inhibitors). The ryanodine receptor was immunoprecipitated by adding 2μl of anti-RyR antibody (5209) and rotating the sample for 1hr at 4°C. The sample was incubated with 40μl of Protein A Sepharose beads and rotated for 1hr at 4°C. After washing the beads with 500μl RIPA buffer three times, the resulted pellet was resuspended in 15μl of 2X SDS sample buffer and boiled for 5 min.

[00188] For Western Blot Analysis, proteins were size fractionated on SDS-PAGE 4-20% gradient (BioRad). Immunoblots were developed with anti-FKBP and anti-RyR antibody or anti-phosphorylated FKBP.

EXAMPLE 4–EFFECTS OF S107 ON SPATIAL LEARNING AND COGNITIVE FUNCTION

[00189] Experiments were performed to determine whether the compounds described herein cross the blood brain barrier and enhance binding of calstabin to ryanodine receptors in the brain. Figure 1 shows the results of Western blots performed on RyR immunoprecipitated from the tissue samples indicated (i.e. heart, soleus muscle, mid-brain, and cerebellum). As illustrated in Figure 1, the compound S107 crosses the blood brain

barrier and restores *in vivo* binding of calstabin to RyR in both the mid-brain and the cerebellum, following depletion of calstabin from the RyR complex by treatment of the mice with isoproterenol ("ISO") by chronic infusion for 5 days. RyR was immunoprecipitated using an antibody to RyR, and the presence of calstabin in the immunoprecipitates was detected using an antibody to calstabin. The figure shows that the compound S107 penetrates the brain and restores *in vivo* binding of calstabin to RyR. Thus, S107 has calstabin rebinding activity in the brain.

[00190] Figure 2 provides a schematic representation of *in vivo* experiments used to test the effect of S107 on cognitive function in mice, using the Morris water maze system (described below in Figure 3). 16 wild type C57BL/6J 3-month-old mice, pairwise-matched for sex, age, and body weight, were randomized to either S107 treatment (10 mg/ml; 0.25 μl/hr subcutaneous osmotic pump) or "vehicle" (25% DMSO in dH_2O) treatment groups. Two days after initiation of treatment, mice were subject to an exercise regimen for 21 days, and effect of S107 treatment was assayed by the weekly protocol as described below. Mice were sacrificed after 21 days for performing biochemistry, calcium imaging and *ex vivo* function studies.

[00191] Figure 3 (A) provides a schematic representation of *in vivo* experiments used to test the effect of S107 on learning in the Morris water maze system. The layout of the water maze system consists of a circular water tank divided into four quadrants (labeled 1 thru 4 in Figure 3, with four hidden platforms (labeled 5 to 8 in Figure 3). The following protocol was followed: Day 1: mice trained to find "hidden" platform with visible marker on platform from random starting location. On days 2-4, the visible cue was removed, and mice were repeatedly challenged to find hidden platform at target 5 in quadrant 1. The time taken for each mouse to reach the target, i.e. the "latency," was recorded. On day 5, the previous day's protocol was repeated, then the hidden platform was removed, and each mouse's movements recorded to quantify time in various target regions. The protocol was repeated in week 2. The bar graphs at the bottom of Figure 3 show the latency to target(s) (panel B) and mean velocity (cm/s) (panel C) for the vehicle and S107 treated groups at the end of the 21-day testing period.

[00192] The platform was then removed, and the swimming pattern of the mice was assessed at the end of the 21-day testing period. Figure 4 shows a trend towards improved learning or increased persistence in S107-treated mice as compared to vehicle. Figure 5

provides graphical data from the above experiments and shows a trend towards altered behavior consistent with improved learning and persistence in the S107-treated mice. p was approximately 0.2 vs. control (n = 8 in both groups). The difference in permanence times between S107-treated and vehicle-treated mice does not appear to be due to swimming differences during the 2-minute probe learning assay.

[00193] Figure 6 shows biochemical data for mice subjected to an exercise regimen in the absence and presence of S107 at the end of the 21-day testing period. Ryanodine receptor (types 1 and 2) was immunoprecipitated from whole brain microsomes. Immunoprecipitates were separated by 4-20% PAGE and analyzed for total RyR, PKA phosphorylated RyR, and calstabin. The figure shows exercised-induced RyR1 and RyR2 phosphorylation, accompanied with reduction in calstabin 1 or 2 binding. Treatment with S107 restores the binding of calstabin to RyR in exercised mice.

EXAMPLE 5 –EFFECTS OF RESTRAINT STRESS ON PKA PHOSPHORYLATION AT DIFFERENT STRESS PERIODS

[00194] Figures 7-10 illustrate the effect of restraint stress on PKA phosphorylation at different stress periods.

[00195] Restraint Stress Model: Chronic stress has been found to induce PKA phosphorylation of ryanodine receptors (RyRs) in cardiac (RyR2) and skeletal (RyR1) muscle cells. The effects of chronic stress on PKA phosphorylation of RyRs in the brain, however, have not been explored. The Restraint Stress Model is designed to investigate whether chronic stress induces PKA phosphorylation of neuronal RyRs. As shown in Figure 7, twelve C57BL/6J wild type male mice were assigned to different stress groups (n=2/group), generating 6 groups. Five of the 6 groups were stressed and sacrificed at the end of each stress period: 1, 5, 10, 14, and 21 days of stress (respectively 1D, 5D, 10D, 14D and 21D). The remaining group served as control (0D) that was not restrained, and was sacrificed together with the 1D group. Subjects in each stress group were restraint stressed in Plexiglas restrainer tubes (10 x 2 ½ x 3 ¾ cm) 2 hr in the morning and 2 hr in the afternoon of each stress period. The two nonstressed control subjects were handled in their home cage. At the end of each stress period, subjects were sacrificed (sac) by CO_2 and their brains were immediately removed and frozen for later immunoblot analysis. RyR2 was immunoprecipitated from whole brain microsomes.

[00196] Figure 8 shows the results of PKA phosphorylation of RyR2 channels in brain following restraint induced stress in mice. The mice were restrained for time periods as indicated. Ryanodine Receptor (type2) was immunoprecipitated from whole brain microsomes. Immunoprecipitates were separated by 4-20% PAGE and analyzed for total RyR2, PKA Phosphorylated RyR2, and calstabin2. The figure shows stress-induced RyR2 phosphorylation, accompanied with reduction in calstabin 2 binding.

[00197] Figure 9 is a bar graph summarizing the relative amounts of PKA phosphorylation of RyR2 from Figure 8. The relative phosphorylation of RyR2 is represented using arbitrary units. A one-way ANOVA shows that there was a significant difference between groups [$F(5,6) = 27.58$, $P < 0.0005$]. Fisher's LSD *post hoc* test reveals that 14 and 21 days of chronic restraint stress (CRS) induced the highest PKA phosphorylation of RyR2 in the brain, where *** ($P < 0.001$) and ** ($P < 0.01$) compared with nonstressed controls (0 days).

[00198] Figure 10 is a bar graph summarizing the relative amounts of calstabin2 bound to RyR2 from Figure 8. A one-way ANOVA also shows a group difference between the stress periods [$F(5,6) = 5.91$, $P < 0.037$]. Fisher's LSD post hoc test reveals that only the 21 days of CRS showed the lowest calstabin2 binding to the RyR2 where * ($P < 0.05$) compared with nonstressed controls (0 days).

CLAIMS

1. A method of treating a neuropathy, seizures, or a cognitive condition, or improving cognitive function, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound of Formula I, or enantiomers, diastereomers, tautomers, pharmaceutically acceptable salts, hydrates, solvates, complexes, metabolites, or prodrugs thereof, or any combination thereof.

2. The method of claim 1, wherein the compound is selected from the group consisting of S1, S2, S3, S4, S5, S6, S7, S9, S11, S12, S13, S14, S19, S20, S22, S23, S24, S25, S26, S27, S36, S37, S38, S40, S43, S44, S45, S46, S47, S48, S49, S50, S51, S52, S53, S54, S55, S56, S57, S58, S59, S60, S61, S62, S63, S64, S66, S67, S68, S69, S70, S71, S72, S73, S74, S75, S76, S77, S78, S79, S80, S81, S82, S83, S84, S85, S86, S87, S88, S89, S90, S91, S92, S93, S94, S95, S96, S97, S98, S99, S100, S101, S102, S103, S104, S105, S107, S108, S109, S110, S111, S112, S113, S114, S115, S116, S117, S118, S119, S120, S121, S122, and S123.

3. The method of claim 1, wherein the compound is selected from the group consisting of S101, S102, S103, S104, S105, S107, S108, S109, S110, S111, S112, S113, S114, S115, S116, S117, S118, S119, S120, S121, S122, and S123.

4. The method of claim 1, wherein the compound is S107.

5. The method of claim 1, wherein the compound crosses the blood brain barrier and penetrates the brain.

6. The method of claim 1, wherein the subject is a human.

7. The method of claim 1, wherein the subject is suffering from, or at risk of developing, a neuropathy.

8. The method of claim 7, wherein the neuropathy is a peripheral neuropathy or a central neuropathy.

9. The method of claim 7, wherein the neuropathy is associated with a condition selected from the group consisting of vestibular neuropathy, optic neuropathy, optic nerve neuropathy, retinal neuropathy, diabetic neuropathy, alcoholic neuropathy, Charcot-Marie-Tooth disease (CMT), Friedreich's ataxia, Gullain-Barre syndrome, polyarteritis nodosa, sarcoidosis, systemic lupus erythematosus, rheumatoid arthritis, sjogren syndrome, HIV infection, syphilis infection, herpes infection, hepatitis infection, colorado tick fever infection, diptheria infection, leprosy, Lyme disease, bacterial infection, viral infection, inflammatory processes, exposure to toxins, treatment with drugs, treatment with chemotherapeutic drugs, cancer, nutritional deficiency, vitamin B-12 deficiency, thiamine deficiency, trauma, pressure on a nerve, a heritable condition, demyelination, axonal damage, uremia, amyloidosis, arsenic poisoning, nitrous oxide exposure or heavy metal exposure.

10. The method of claim 1, wherein the subject is suffering from, or at risk of developing, a seizure condition.

11. The method of claim 10, wherein the seizure condition is selected from the group consisting of epilepsy, a non-epileptic seizure condition, partial onset seizures, focal onset seizures, distributed seizures, generalized seizures, simple partial seizures, complex partial seizures, myoclonic seizures, clonic seizures, tonic seizures, tonic-clonic seizures, atonic seizures, petit mal seizures, grand mal seizures, Jacksonian seizures, psychomotor seizures, temporal-lobe seizures, non-epileptic seizures, unprovoked seizures, alcoholic seizures, infantile spasms, West syndrome, benign childhood epilepsy with centro-temporal spikes, benign rolandic epilepsy, benign childhood epilepsy with occipital paroxysms, juvenile myoclonic epilepsy (JME), temporal lobe epilepsy, frontal lobe epilepsy, Lennox-Gastaut syndrome, occipital lobe epilepsy, fetal alcohol spectrum disorder (FASD), psychogenic seizures, and febrile convulsions.

12. The method of claim 1, wherein the subject is suffering from, or at risk of developing, a cognitive disorder.

13. The method of claim 12, wherein the cognitive disorder is selected from the group consisting of dementia, delirium, amnesia, aphasia, Alzheimer's disease, vascular

dementia, multi-infarct dementia, Binswanger's disease, dementia with Lewy bodies (DLB), alcohol-induced persisting dementia, frontotemporal lobar degenerations (FTLD), Pick's disease, frontotemporal dementia, frontal variant FTLD, semantic dementia, temporal variant FTLD, progressive non-fluent aphasia, Creutzfeldt-Jakob disease, Huntington's disease, Parkinson's disease, AIDS dementia complex, an attention disorder, attention-deficit disorder (ADD), attention-deficit hyperactivity disorder (ADHD), stress-induced cognitive dysfunction, age related cognitive dysfunction, and post-traumatic stress disorder.

14. The method of claim 1, wherein the cognitive function to be improved is memory.

15. The method of claim 14, wherein the memory is long-term memory or short-term memory.

16. The method of claim 1, wherein the cognitive function to be improved is learning.

17. The method of claim 1, wherein the cognitive function to be improved is attention.

18. The method of claim 1, wherein the compound is administered by a route selected from the group consisting of parenteral, enteral, intravenous, intraarterial, intraspinal, intra, intraosseal, intracutaneous, subcutaneous, intradermal, subdermal, transdermal, intrathecal, intramuscular, intraperitoneal, intrasternal, parenchymatous, oral, sublingual, buccal, rectal, vaginal, inhalational, and intranasal.

19. The method of claim 1, wherein the compound is administered using a drug-releasing implant.

20. The method of claim 1, wherein the compound is administered to the subject at a dose sufficient to restore binding of calstabin to a RyR.

21. The method of claim 1, wherein the compound is administered to the subject at a dose sufficient to enhance binding of calstabin to a RyR.

22. The method of claim 1, wherein the compound is administered to the subject at a dose of from about 0.01 mg/kg/day to about 20 mg/kg/day.

23. A method of treating a neuropathy, seizures, or a cognitive condition, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound that decreases the open probability of a RyR channel.

24. A method of treating a neuropathy, seizures, or a cognitive condition, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound that decreases Ca2+ current through a RyR channel.

25. A method of treating a neuropathy, seizures, or a cognitive condition, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound that decreases calcium leak through a RyR channel.

26. A method of treating a neuropathy, seizures, or a cognitive condition, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound that increases the affinity with which calstabin binds to a RyR.

27. A method of treating a neuropathy, seizures, or a cognitive condition, in a subject in need thereof, comprising administering to the subject a therapeutically effective amount of a compound that decreases dissociation of calstabin from a RyR.

28. The method according to any one of claims 23-27, wherein the RyR is selected from the group consisting of RyR1, RyR2, and RyR3.

29. The method according to any one of claims 23-27, wherein the compound is represented by the structure of Formula I and is able to penetrate the brain.

30. Use of a compound of Formula I for the manufacture of a medicament to treat a condition selected from the group consisting of a neuropathy, seizures and a cognitive condition.

31. Use of a compound of Formula I for the manufacture of a medicament to improve cognitive function.

Figure 1

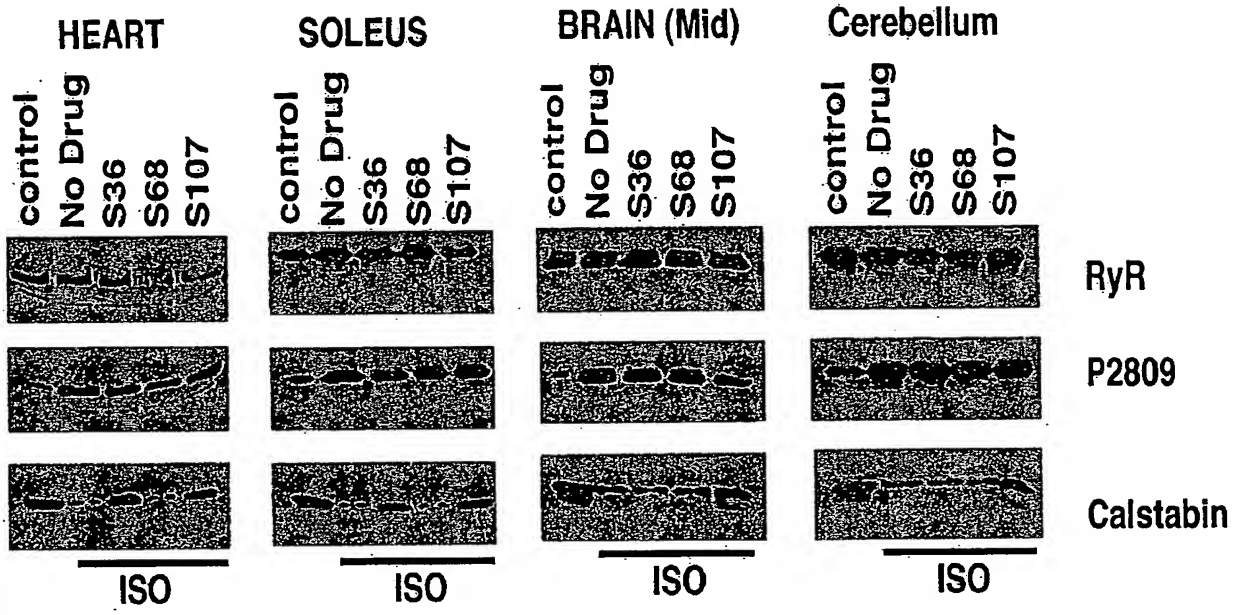

HEART
SOLEUS
BRAIN (Mid)
Cerebellum
control
No Drug
S36
S68
S107
RyR
P2809
Calstabin
ISO

Figure 2

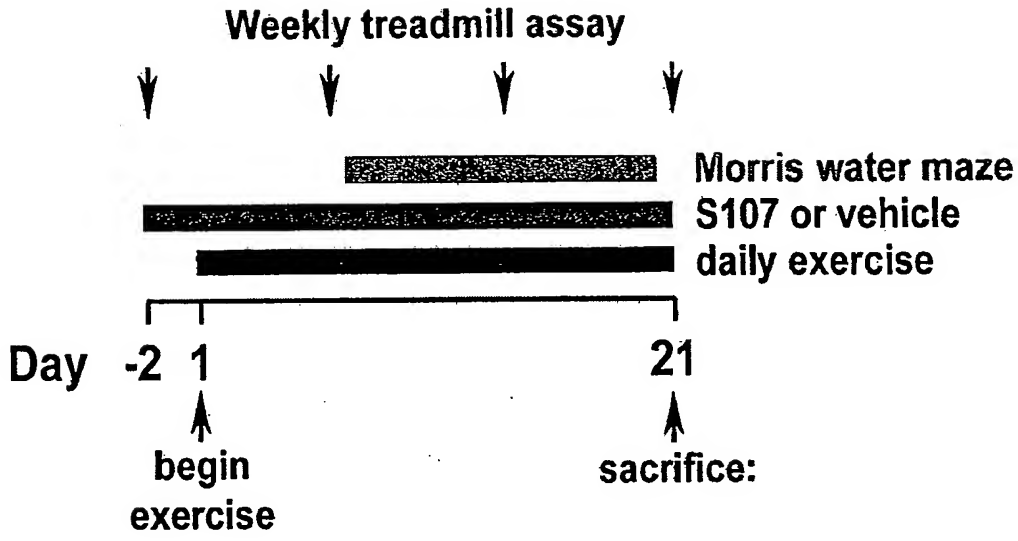

Weekly treadmill assay
Morris water maze
S107 or vehicle
daily exercise
Day -2 1
21
begin exercise
sacrifice:

Figure 3

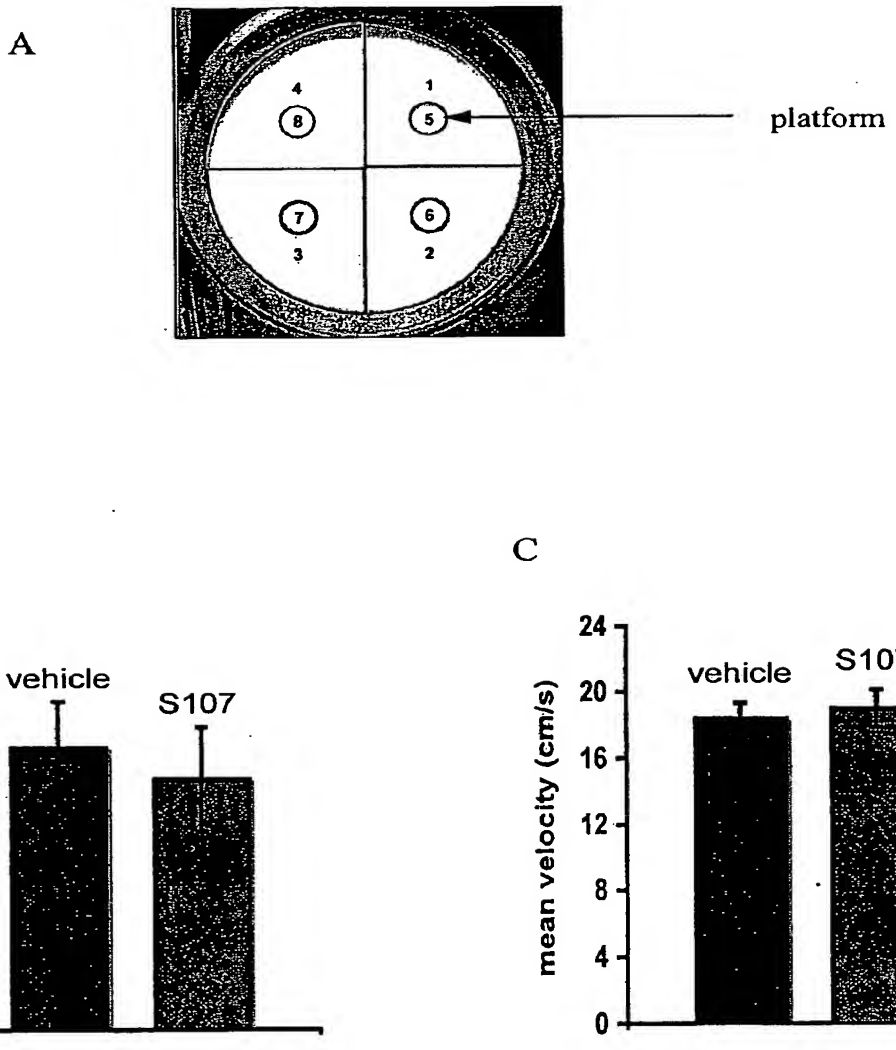

A
4
1
8
5
platform
7
6
3
2
B
latency to target (s)
12
10
8
6
4
2
0
vehicle
S107
C
mean velocity (cm/s)
24
20
16
12
8
4
0
vehicle
S107

Figure 4

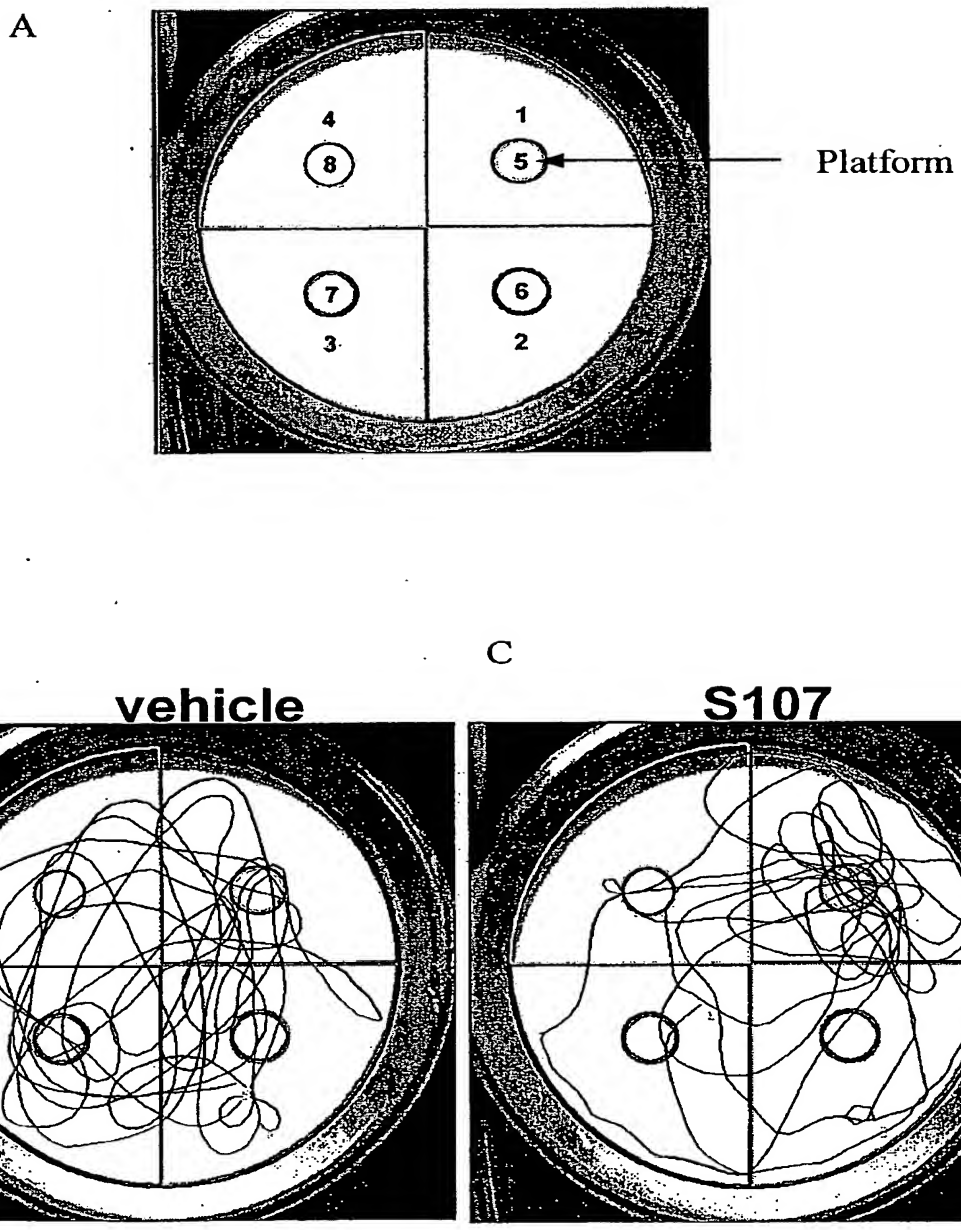
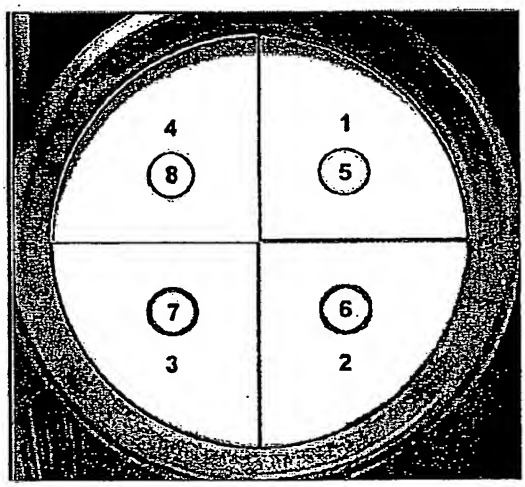


Figure 5

A


4
1
8
5
7
6
3
2

B

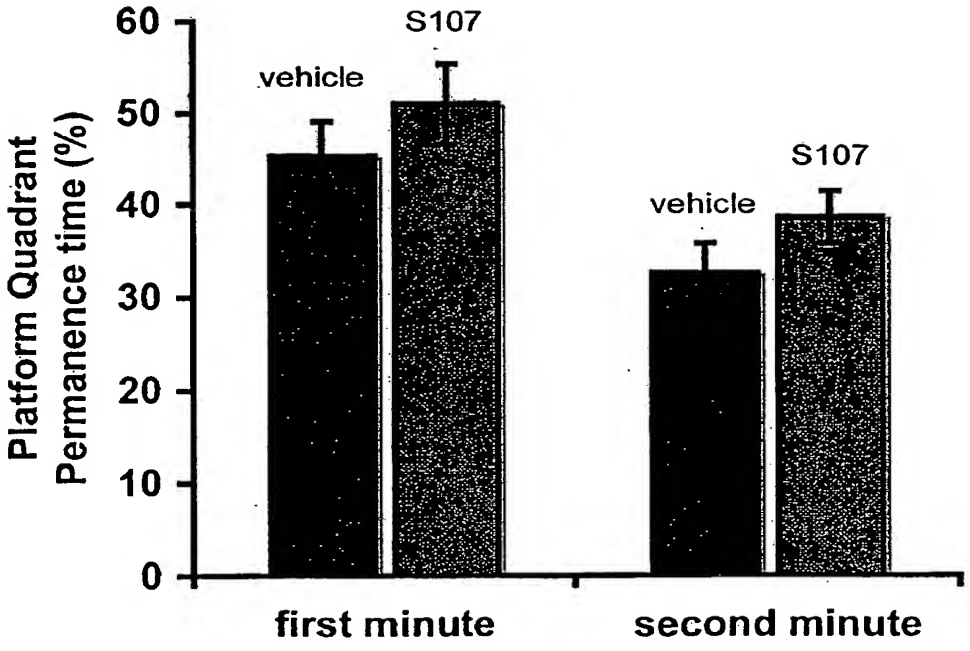

60
50
40
30
20
10
0
Platform Quadrant Permanence time (%)
vehicle
S107
vehicle
S107
first minute
second minute

Figure 6

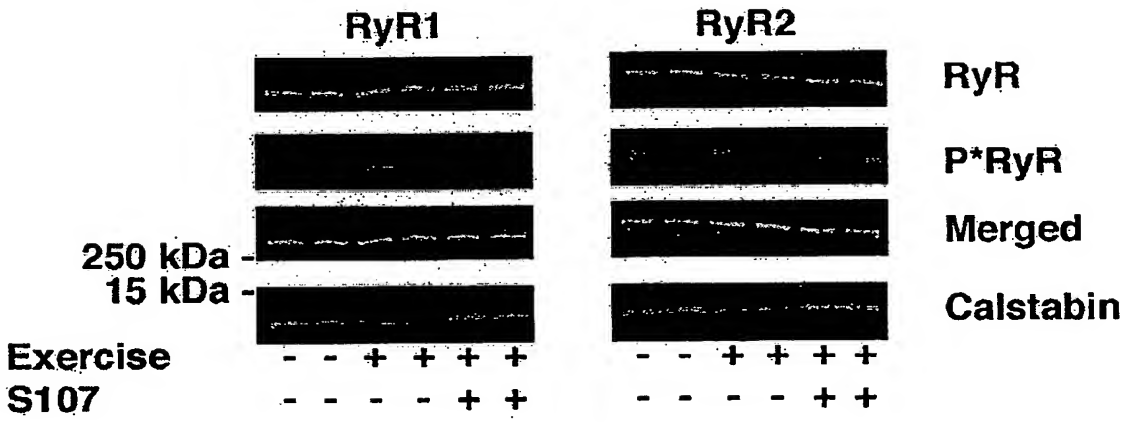

RyR1
RyR2
RyR
P*RyR
Merged
Calstabin
250 kDa
15 kDa
Exercise - - + + + + - - + + + +
S107 - - - - + + - - - - + +

Figure 7

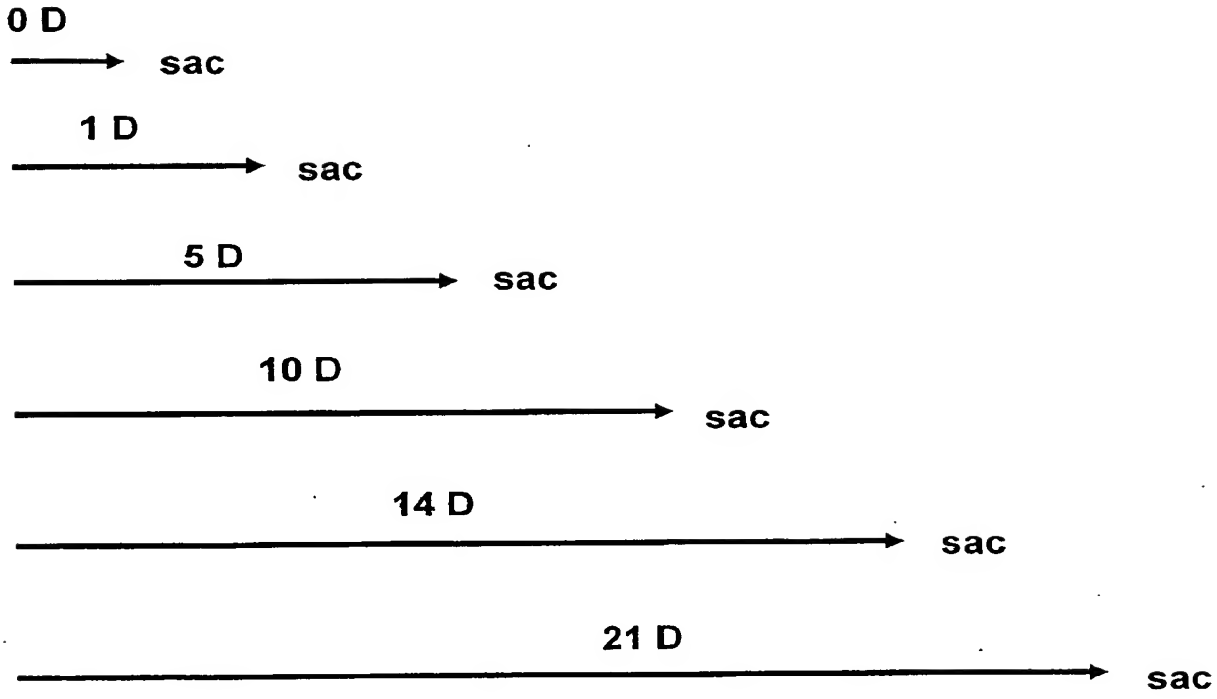


Figure 8

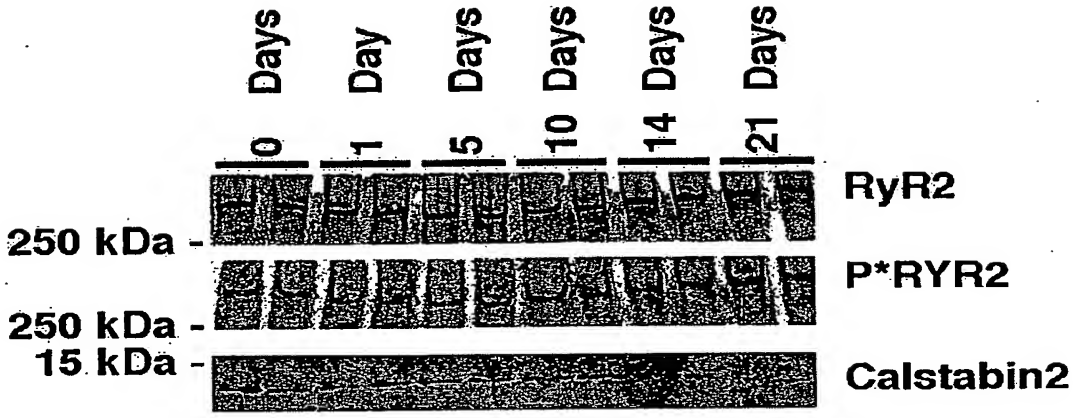

0 Days
1 Day
5 Days
10 Days
14 Days
21 Days
RyR2
250 kDa -
P*RYR2
250 kDa -
15 kDa -
Calstabin2

Figure 9

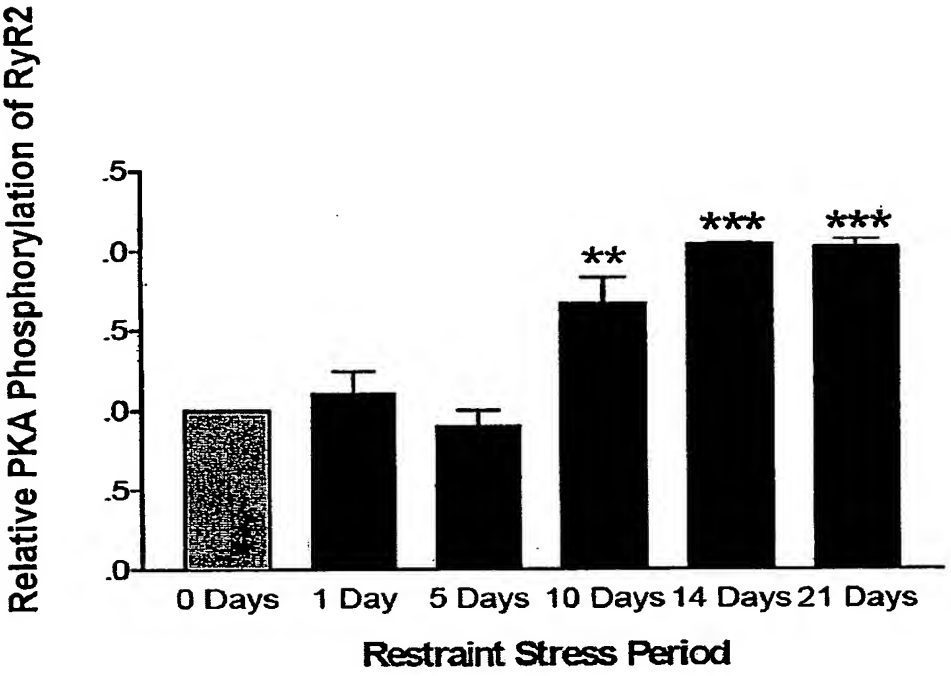
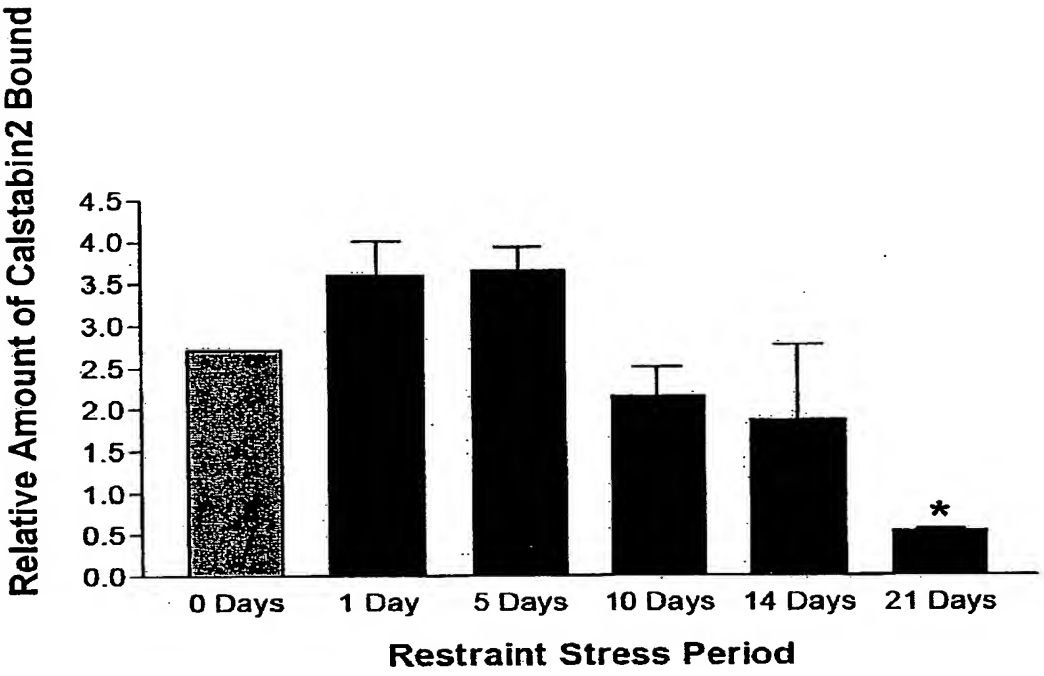

Relative PKA Phosphorylation of RyR2
.5
.0
.5
.0
.5
.0
**
***
***
0 Days
1 Day
5 Days
10 Days
14 Days
21 Days
Restraint Stress Period

Figure 10


Relative Amount of Calstabin2 Bound
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
*
0 Days
1 Day
5 Days
10 Days
14 Days
21 Days
Restraint Stress Period